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Study Report

Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries: Immune-mediated diseases

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PASS information

Title	**Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries: Immune-mediated diseases**
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Research question objectives	**Primary objectives – vaccine safety objectives** To conduct a feasibility study on the association between COVID-19 vaccination and selected immune-mediated diseases (both-new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries. **Secondary objectives – outcome after infection objectives:** To evaluate the association between COVID-19 infection and selected immune-mediated diseases (both-new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries.
Countries of study	Denmark, Finland, Norway, Sweden
Author	Anders Hviid, Kristina Dvoncova
MARKETING AUTHORIZATION HOLDER(S)	Not applicable.

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1. ABSTRACT

Title: Association between COVID-19 vaccines and paediatric safety outcomes in children and adolescents aged 5-19 years in the Nordic countries: Immune-mediated diseases

Keywords: COVID-19, vaccine safety, adverse events, children, nationwide cohorts, Nordic countries.

Rationale and background: There is a clear need for a comprehensive mapping of the safety of COVID-19 vaccination in children/adolescents focusing on rare adverse events of special interest including immune-mediated diseases which can debut early in life.

Research question and objectives: The overall aim of this project was to take advantage of the Nordic setting (Denmark, Finland, Norway, Sweden) and conduct a study on the possible associations between COVID-19 vaccination and selected immune-mediated diseases in children/adolescents supporting feasibility and recommendations for potential future studies addressing similar research questions, on COVID-19 or other vaccines.

Primary objectives – vaccine safety objectives: To conduct a feasibility study on the association between COVID-19 vaccination and selected immune-mediated diseases (both new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries.

Secondary objectives – outcome after infection objectives: To evaluate the association between COVID-19 infection and selected immune-mediated diseases (both-new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries.

Setting: Nationwide register-based cohort studies in Denmark, Finland, Norway and Sweden during the study period 1 January 2021 to 31 December 2022. We took full advantage of the nationwide and longitudinal nature of the Nordic cohorts and leveraged two complementary survival analysis approaches; 1) contemporary cohort analyses providing adjusted relative risks and excess risks, and 2) self-controlled case series analyses nested in the cohorts providing relative risks, which are by design not confounded by time-independent covariates.

Population: The source cohorts consisted of all individuals 5 to 19 years of age during the study period of 1 January 2021 to 31 December 2022 in Denmark, Finland, Norway, and Sweden. Having a positive RT-PCR test before the study started was an exclusion criterion, as well as a censoring criterion during follow-up in the primary analyses of

vaccine safety. In the secondary analyses of infection risk, vaccination was an exclusion criterion before the study started and a censoring criterion during follow-up.

Study size: The Nordic countries contributed with a total population of 5,029,084 children/adolescents. Among the European countries that have implemented childhood/adolescent COVID-19 vaccination, the Nordic countries have had uptakes at the upper end of the range.

Variables and data sources: The outcomes of interest in the analyses of new-onset disease were autoimmune hepatitis, Guillain-Barré syndrome and type 1 diabetes. The outcomes of interest in the analyses of disease flares were juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes. These were selected to include outcomes with both acute and more insidious onset, both transient and chronic conditions and conditions with varying incidence rates. Data sources were nationwide demography and health registers within each participating country. The outcomes of interest were identified in hospitalisation registers based on ICD-10 codes. A flare was defined as a hospital visit related to a pre-existing immune-mediated disease. The Pfizer/BioNTech (BNT) mRNA vaccine was almost exclusively used in this setting. BNT1 denotes the first dose, BNT1BNT2 denotes the second dose in a homologous primary course schedule and BNT1BNT2BNT3 denotes the booster dose in a homologous schedule.

Results: We observed no robust associations between BNT-vaccination and new onset of autoimmune hepatitis, Guillain-Barré syndrome or type 1 diabetes in either the 28-day- or the 180-day main risk period. We did observe a strong, but statistically imprecise association between SARS-CoV-2 infection and Guillain-Barré syndrome. The association was strongest in the 28-day main risk period (contemporary cohort RR 15.10, 95% CI, 1.11-205.94) and still present in the 180-day main risk periods (contemporary cohort RR 3.85, 1.33-11.14). In cohorts of patients with a previous diagnosis of juvenile rheumatoid arthritis, multiple sclerosis or type 1 diabetes, we observed no robust support for an increased risk of hospital visits following BNT vaccination or infection in either the 28-day- or the 180-day main risk period.

Discussion: Very few studies have evaluated the safety of COVID-19 vaccination in children and adolescents with respect to immune-mediated diseases both in the context of new onset disease and disease flares. Immune-mediated diseases are rare in childhood and adolescents which is reflected in the statistical precision of many of our estimates despite this being a large multi-country evaluation. The results from two different analytical approaches complement each other and support the internal validity of our study. The study of immune-mediated diseases in the observational setting has a number of limitations. Foremost is the lag between disease onset, symptom onset and first diagnosis. This requires careful consideration of main risk period definitions and

careful interpretation of results. The evaluation of risk of disease flares is limited by the lack of available information on disease activity when chart review and detailed disease specific registers or databases are not available. The alternative use of hospital visits is feasible but requires careful consideration of alternative explanations of any observed increases.

Conclusion: The current study provides much needed and reassuring evidence that BNT vaccination does not appear to be associated with immune-mediated disease onset or activity in children and adolescents. The study demonstrates the feasibility of conducting vaccine safety studies for all vaccines used in these age-groups, and provides recommendations for best practices in the design and conduct of these studies.

Marketing authorization holder: Not applicable.

Names and affiliations of principal investigators:

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2. LIST OF ABBREVIATIONS

AZD1222	Oxford-AstraZeneca adenovirus viral vector vaccine, Vaxzevria
BNT	BioNTech-Pfizer mRNA vaccine, Comirnaty
mRNA-1273	Moderna mRNA vaccine, Spikevax
ICD-10	International classification of diseases revision 10
COVID-19	Coronavirus disease 2019
RT-PCR	Reverse transcription polymerase chain reaction
SCCS	Self-controlled case series analysis

3. INVESTIGATORS

All main responsible parties including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country/organisation in which the study was performed and other relevant study sites are presented in the table below.

Name	**Professional Title**	**Affiliation and address**
Jesper Kjær	Director of Department	Danish Medicines Agency, Data Analytics Centre, Axel Heides Gade 1, DK-2300 Copenhagen S, Denmark
Niels Henrik Meedom	Project manager and fundraiser	
Anders Hviid	Head of Department, Professor	Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark Department of Drug Design and Pharmacology, Pharmacovigilance Research Center, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen Ø, Denmark
Petteri Hovi	Research manager	Finnish Institute for Health and Welfare, Mannerheimintie 166, Helsinki, Finland, POBox 30, FI-00271

Øystein Karlstad	Senior researcher	Norwegian Institute of Public Health, Department of Chronic diseases, P.O.Box 222-Skøyen, NO-0213 Oslo, Norway
Rickard Ljung	Professor	Swedish Medical Products Agency, Division of Use and Information, SE3751 03 Uppsala, Sweden

The table below presents all named scientific personnel in the study group together with their respective role in the study.

Name	**Affiliation**	**Role in the study**	**Description of the function**
Anders Hviid	SSI (DK), KU (DK)	Principal investigator	Overall coordination and oversight of the study; responsible for the submission of deliverables. Local scientific coordination Denmark.
Kristina Dvoncova	SSI (DK)	Junior epidemiologist	Local project management, help with drafting study protocols and -report.
Emilia Myrup Thiesson	SSI (DK)	Statistician	Conducts the Danish analyses and meta-analyses of country-specific results.
Jørgen Vinsløv Hansen	SSI (DK)	Statistician	Conducts the Danish analyses and statistical supervision.
Petteri Hovi	THL (FI)	Senior epidemiologist	Local scientific coordination Finland, review and approval of deliverables.
Hanna Nohynek	THL (FI)	Senior epidemiologist	Scientific supervision.
Tuomo Nieminen	THL (FI)	Statistician	Conducts the Finnish analyses.
Øystein Karlstad	FHI (NO)	Senior epidemiologist	Local scientific coordination Norway, review and approval of deliverables.
Hanne Løvdal Gulseth	FHI (NO)	Senior epidemiologist	Scientific supervision.

German Tapia	FHI (NO)	Senior epidemiologist	Conducts the Norwegian analyses.
Inger Johanne Bakken	FHI (NO)	Statistician	Conducts the Norwegian analyses.
Rickard Ljung	SWE MPA (SE)	Senior epidemiologist	Local scientific coordination in Sweden, review and approval of deliverables.
Nicklas Pihlström	SWE MPA (SE)	Statistician	Conducts the Swedish analyses.
Morten Andersen	KU (DK)	Senior epidemiologist	Scientific supervision.

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestones	Planned date	Actual date	Comments
Start of data collection	3 August 2022	3 August 2022	
End of data collection	1 October 2022	1 October 2022	
Study Plan	5 September 2022	5 September 2022	
Study Protocol (posted on EU-PAS register).	11 November 2022	16 December 2022	Incorporating minor comments from reviewers.
Registration in the EU-PAS register	11 November 2022	16 December 2022	Incorporating minor comments from reviewers.
Study report (final report will be posted on the EU-PAS register once approved by EMA and contributing parties).	3 February 2023	14 April 2023	Delay due to difficulty in running the analyses at some sites
Manuscript(s) ready for submission	3 March 2023	17 April 2023	

6. RATIONALE AND BACKGROUND

The initial phase 3 clinical trials demonstrating the efficacy and safety of the mRNA- and adenovirus viral vector vaccines were conducted in adults only, as were the later trials of inactivated vaccines.[1–5] Following the adult clinical trials, clinical trials in children and adolescents of decreasing age have been conducted. This includes two phases 3 trials of the BNT162b2 (Pfizer-BioNTech) vaccine in 12 to 15-year-olds and in 5 to 11-year-olds, respectively, and a phase 3 trial of the mRNA-1273 (Moderna) vaccine in 12 to 17-year olds.[6–8] While these trials have reported satisfactory efficacy and safety, the number of participants has been modest (1517, 1131 and 2489 were vaccinated in the BNT162b2 trial of 5 to 11-year-olds, the BNT162b2 trial of 12 to 15-year-olds and the mRNA trial of 12 to 17-year-olds, respectively) and the follow-up periods short. Thus, there is little clinical trial evidence with respect to rare adverse events or long-term adverse events following COVID-19 vaccination in children and adolescents. Reassuringly, no major safety issues have appeared during the autumn/winter vaccinations of children/adolescents in 2021/22. However, there is a clear need for a comprehensive mapping of the safety of COVID-19 vaccination in children/adolescents focusing on rare adverse events of special interest. This should include immune-mediated disease which debut in early life. Vaccine safety studies on immune-mediated diseases in children and adolescents are challenging to design and conduct. Thus, there is also a clear need for safety studies of immune-mediated outcomes in these age-groups that demonstrates feasibility and provides recommendations on best practices for study design and conduct.

Immune-mediated diseases following COVID-19 vaccination

Immune-mediated diseases are often linked to childhood vaccinations due to temporal association purely by chance since many of these conditions have onset in childhood or early adulthood. However, there are a number of associations that are likely to be causal such as the 1976 swine flu vaccine and Guillain-Barré syndrome, and H1N1 influenza vaccination and narcolepsy.[9] This necessitates careful surveillance of immune-mediated adverse events following vaccination. Case reports and spontaneous reports have already linked several autoimmune conditions, such as Bell’s palsy, Guillain-Barré syndrome and transverse myelitis, to COVID-19 vaccination, but few analytical observational studies have been conducted. In an observational study of primary care records from the United Kingdom and Spain, no safety signals were observed between COVID-19 vaccines and the immune-mediated neurological events of Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis.[10] However, this study only considered adults and the use of primary care records is not ideal for the

identification of conditions most likely ascertained in specialist care. In a Hong Kong study of 3.9 million individuals 16 years of age or older, an association between the first dose of BNT162b2 and narcolepsy and related disorders was reported.[11] In another Hong Kong study of 396,800 adolescents (12 to 18 years of age), the risk of a range of adverse events of special interest (including several autoimmune diseases) was compared among vaccinated individuals within 28-days of vaccination and unvaccinated individuals.[12] No associations were detected, but estimates were based on very few cases precluding strong conclusions. An important limitation of currently available observational studies is the lack of sufficient follow-up outside of the immediate weeks following vaccination; the new onset of immune-mediated disease may be insidious and long-term follow-up is needed to fully evaluate the safety of vaccines with respect to immune-mediated diseases. In the current study, we were able to provide follow-up for immune-mediated diseases for up to 6 months after vaccination.

Selection of study outcomes

In our study, we included 5 different immune-mediated diseases: Autoimmune hepatitis, Guillain-Barré syndrome, type 1 diabetes, juvenile rheumatoid arthritis, and multiple sclerosis. These have been selected based on at least one of the following criteria, a) previous possible link to COVID-19 vaccination (confirmed or not), or b) previous possible link to childhood vaccinations (confirmed or not). Guillain-Barré syndrome, autoimmune hepatitis and type 1 diabetes have all been linked to COVID-19 vaccination.[13–15] Multiple sclerosis and juvenile rheumatoid arthritis have both been linked to childhood vaccinations.[16,17] We also selected outcomes such that we include outcomes with both acute and more insidious onset, both transient and chronic conditions and conditions with varying incidence rates.

7. RESEARCH QUESTIONS AND OBJECTIVES

The overall aim of this project was to take advantage of the Nordic setting (Denmark, Finland, Norway, Sweden) to conduct a feasibility study of the possible associations between COVID-19 vaccination in children/adolescents and selected immune-mediated diseases.

Primary objectives – vaccine safety objectives:

To conduct a feasibility study on the association between COVID-19 vaccination and selected immune-mediated diseases (both new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries.

Secondary objectives – risk/benefit evaluation objectives:

To evaluate the association between COVID-19 infection and selected immune-mediated diseases (both new onset and flares) in children/adolescents aged 5 to 19 years in the Nordic countries.

8. AMENDMENTS AND UPDATES

Number	Date	Section	Amendment or update	Reason
Protocol 1.2.	17-11-2022	Page 1 Page 5-6 Page 8 Page 10 Page 11-14 Page 42-45 Page 48-49 All pages	Exclusion of general considerations and timely assessment from study objectives. Research question and objectives modified in the abstract. Milestones of the project were modified according to the EU PASS requirements. Expansion of the rationale for selection of the immune-mediated disease outcomes. Description of study design updated. Risk periods of interest was elaborated. Description of statistical analyses updated, including statistical power. A new section on the "general considerations for timely assessment of vaccine safety" added. Typos correction and redundant text removal.	Incorporating the major and minor comments from EMA assessment of study protocol version 1.1.
Study report II	03-04-2023	All pages	Only including 5 selected immune-mediated outcomes	See section 9.2 for a discussion on the exclusion of the pre-

			Only including results from SCCS and contemporary cohort analyses	specified observed vs expected analyses.
dStudy report II	29-04-2023	All pages	Revision according to minor comments from EMA and co-authors	

9. RESEARCH METHODS

9.1 Study setting and period

The study objectives were addressed through nationwide register-data. We constructed country-specific cohorts of 5 to 19 year olds with individual-level information on dates of vaccination and dates of adverse event outcomes together with relevant covariate information. The study period was from 1 January 2021 to 31 December 2022.

The Nordic countries provide a unique setting for the study of COVID-19 vaccine safety in childhood. Firstly, the ubiquitous nationwide demography and health registers, which include COVID-19 vaccination and surveillance registers, has allowed for study cohorts in the current study with a combined size of 5,029,084 million children/adolescents aged 5 to 19 years. Secondly, the Nordic countries have had high vaccine uptake during the vaccination rollouts compared to many other European countries. Thirdly, the Nordic countries all have universal healthcare free of charge, reducing concern about selection bias, and homogeneous data sources, which are easily combined. Fourthly, the organisations representing the Nordic countries in this project have access to near-real-time data, which is a key advantage in the study of rare immune-mediated adverse events that do not necessarily only occur in an acute period following vaccination but necessitates longer follow-up. Finally, the Nordic countries have nationwide hospitalisation registers; most of the study outcomes are best ascertained in the specialised hospital setting in contrast to primary care databases.

9.2 Study design and subjects

We conducted nationwide register-based cohort studies in the four larger Nordic countries (Denmark, Finland, Norway, Sweden). We used two complementary survival analysis methods. The cohort participants were followed from 1 January 2021 and until 31 December 2022 and classified in a time-varying manner according to vaccination (and infection) status. Rates of study outcomes were assessed in pre-defined risk periods (28-days/180-days) of interest following vaccination and compared to unvaccinated follow-up periods. Disease flare risk was evaluated in cohorts of patients with pre-existing immune-mediated diseases.

Main risk periods of interest

We defined two risk periods of interest (short-term and long-term) for new onset of disease and diseases flares - see table below. The distinction between new onsets of short- and long-term immune-mediated disease considers that immune-mediated diseases can have both a relatively acute onset, such as for Guillain-Barré syndrome and a more insidious onset, such as type 1 diabetes. For the study of new-onset events, we

included autoimmune hepatitis and Guillain-Barré syndrome which are both most likely to present acutely in the weeks after an exposure. For the study of disease flares, we included multiple sclerosis and juvenile rheumatoid arthritis, both diseases where flares are not uncommon. Type 1 diabetes is the most common autoimmune disease in childhood, why we included it in the new-onset analysis, and it is a chronic condition, why we also included it in the flares analysis.

	Main risk period of interest
I. Short-term risk period	Day 0 – 27
II. Long-term risk period	Day 0 – 179

Justification of risk periods

Most available studies of COVID-19 vaccine safety have focused on an acute risk period following vaccination such as 28- or 42-days.[18,19] This has allowed for the identification of adverse events such as thromboembolism with thrombocytopenia syndrome and myocarditis.[20,21] These durations are also consistent with previous vaccine safety work on e.g. Guillain-Barré syndrome. In a previous population-based cohort study in the United Kingdom and Spain (with 8,330,497 participants), a 21-day risk period after vaccination was used for assessment of the association between COVID-19 vaccination, SARS-CoV-2 infection and risk of immune-mediated neurological events.[22] Another study from Israel evaluating both new onset disease and flares for 27 study outcomes after COVID-19 vaccination used a 28-day risk period after vaccination.[18]

For outcomes with a more insidious onset or significant lag between onset of symptoms and diagnosis, a longer risk period is appropriate. In our study, the choice of a 180-day risk period considered the scale of the typical duration of follow-up that we could expect in our study (9 to 12 months) while still providing reasonable time for either an insidious onset or diagnostic lag.

The acute risk periods started on day 0 (the day of vaccination) and lasted up to and including day 27 or 179 corresponding to risk period lengths of 28-days and 180-days (see table above). Infection was a censoring event for the evaluations of vaccination as an exposure and vaccination was a censoring event for the evaluations of infection as an exposure. Similarly, infection before study start resulted in exclusion for the evaluations

of vaccination as an exposure and vaccination before study start resulted in exclusion for the evaluations of infection as an exposure

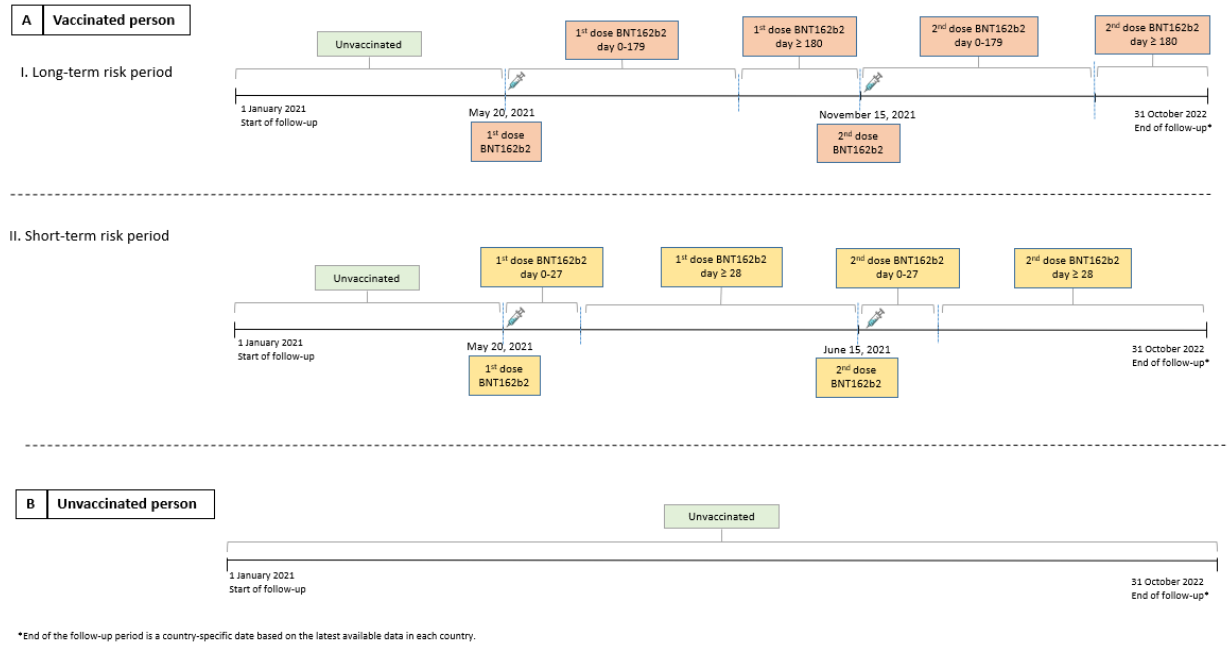
In the figure below (Figure 1) we illustrated different follow-up scenarios according to the main risk period of interest.

Figure 1A (I. Long-term risk period): Example of an individual who was vaccinated with a first dose on 20 May 2021, and followed up 180 days from the first dose, vaccinated with a second dose on 15 November 2021, and followed up 180 days after a second dose.

Figure 1A (II. Short-term risk period): Example of an individual who was vaccinated with a first dose on 20 May 2021, and followed up 28 days from the first dose, vaccinated with a second dose on 15 June 2021, and followed up 28 days after a second dose.

Figure 1B (reference unvaccinated follow-up): Example of an individual who was not vaccinated and was followed up until the end of follow-up.

Figure 1. Schematic Illustrations of Follow-up Time Windows in the Cohort Study



*End of the follow-up period is a country-specific date based on the latest available data in each country.

The following table illustrates the complementary nature of the selected methods together with their advantages and disadvantages in the context of the current study:

Method	Reference follow-up	Estimation	Main advantage	Main disadvantage
Contemporary cohort analysis	Unvaccinated time during the pandemic	Regression, including time-dependent and time-invariant confounder adjustment	Nationwide cohort with less concern about selection and recall bias. Concurrent comparator. Adjustment for confounders.	Relies on the availability of confounder information.
Self-controlled case series	For vaccinated cases: Follow-up time as unvaccinated	Regression, including time-dependent confounder adjustment	No time-invariant confounding by design.	The assumption that having the outcome has no significant influence on the future probability of exposure must be fulfilled.

Observed vs Expected analyses

When planning this study we intended to also include observed vs expected analyses. Observed vs expected analyses compares the observed rates in the main risk periods to expected rates calculated from historical rates taking age and sex into account using standardisation.

In the initial analyses, we observed markedly reduced rates of flares in the observed periods that were incompatible with the results from the two other analytical approaches. We discovered that this was due to critical differences in how wash-out periods were handled, which would bias towards overcounting of flares in the historical period compared to the contemporary period. Since the observed vs expected analyses were planned to be supportive rather than main analyses and in order to make the deadlines for the study deliverables, we chose to drop these analyses. This issue emphasises that when studying flares using designs which compares different time periods, it is critical to ensure that recurring outcomes are ascertained in exactly the same way between periods.

9.3 Study population

The subjects of the study were all individuals 5-to-19-years-of-age during the study period 1 January 2021 to 31 December 2022. Age was defined within each of the two years of follow-up to be calendar year minus birth year. Thus, children born in 2017,

could only contribute follow-up from 1 January 2022 as 5-year-olds and those born in 2002 could contribute follow-up only until 31 December 2021 as 19-year-olds. The Nordic populations comprised 5,029,084 million individuals aged 5-to-19-years with COVID-19 vaccine uptake rates that were higher than many other countries in the European region. One of the key strengths of our approach was the use of nationwide data on whole populations reducing concern about selection bias e.g. by socioeconomic differences in who was enrolled with a specific health service provider.

In the evaluation of flares, we defined patient-specific cohorts. A recording of a diagnosis of the immune-mediated disease under study in the study period or the two years preceding (i.e. 1 January 2019 to 31 December 2022) before exposure, was the inclusion criterion.

9.4 Variables

Vaccination

The Nordic countries implemented national vaccination campaigns against COVID-19 on 27 December 2020, providing free vaccinations to all residents. Phased distribution plans were implemented prioritizing vaccination of individuals at the highest risk of COVID-19 complications and frontline personnel (nursing home residents, healthcare workers, and elderly). Denmark, Finland and Norway almost exclusively used mRNA vaccines after full or partial discontinuation of AZD1222 in March 2021 due to serious but rare events of thrombosis with thrombocytopenia. Sweden used AZD1222 for a majority of the population older than 64 years and mRNA vaccines in other age groups. Ad26.COV2.S has seen very limited use. The Nordic countries have vaccinated around 6 times more individuals with BNT162b2 than with mRNA-1273.

COVID-19 vaccination in children/adolescents in the Nordic countries.

In Denmark, all 5-to-17-year-olds have been recommended two doses; 18-to-19-year-olds have been recommended three doses. Among 5-to-17-year-olds at high risk of severe COVID-19, a third dose has been recommended. Due to the rare occurrences of severely ill children and adolescents from the Omicron variant, the Danish competent authorities adopted changes in the vaccination guidelines. From 1 July 2022, it was not possible for children and adolescents under the age of 18 years to get the first dose of the vaccine, and from 1 September 2022, it was no longer possible for them to get the second dose of the vaccine. Children at high risk of severe COVID-19 was still offered vaccination based on an individual assessment by a doctor.

In Finland, 5-to-11-year-olds who are at high risk of severe COVID-19 or are in close contact with an immunocompromised person have been recommended two doses; it has been possible for all other 5-to-11-year-olds to also get two doses if so desired. Among 12-to-17-year-olds, two doses have been recommended and risk groups have been recommended three doses. The 18-to-19-year-olds have been recommended three doses. On 21 September 2021, THL recommended that only BNT be used for males younger than 30-years-of-age.

In Norway, COVID-19 vaccination for 5-to-11-year-olds was only recommended if they were at a high risk of severe COVID-19 due to underlying medical conditions. In such cases, two doses were recommended. However, for all other 5-to-11-year-olds, vaccination was available at parents discretion. Among 12-to-15-year-olds, one dose has been recommended with a second dose being optional; risk groups have been recommended two doses. Among 16-to-17-year-olds, two doses with a 12-week interval was recommended with a shorter interval between doses for persons in risk groups. The 18-to-19-year-olds were recommended two doses with a third dose being optional; risk groups have been recommended three doses. Only BNT have been available for children and adolescents below 18 years, whereas all males below 30 were recommended to use the BNT vaccine from 6 October 2021 and females under age 30 were given the same advice from 11 January 2022.In Sweden, 12-to-17-year-olds have been recommended two doses with a 4-to-7-week interval. Patients at high risk of severe COVID-19 in this age group have been recommended a third dose. Children 5-11-years-of-age with (severe) immune deficiency or immunosuppressive treatment have also been recommended vaccination. The 18-to-19-year-olds have also been recommended a third dose. Since October 6, 2021, Sweden has not recommended the use of mRNA-1273 for males or females under age 30. For that reason, vaccination schedules including this vaccine (mRNA-1273) are relatively uncommon in the targeted population. Since November 1, 2022, children under 18 years of age were no longer recommended COVID-19 vaccination due to the low risk of serious illness and death from COVID-19. Furthermore, the booster dose was not recommended for children 12-to-17-years-of-age. For high-risk group children, the recommendation to vaccinate remained.

In all of the Nordic countries, the 5-to-11-year-olds that have been vaccinated have received either 1/3 of an adult dose or a specific paediatric formulation with a lower dose.

The primary exposure of interest in our study was the BNT162b2 mRNA vaccine that has been used almost exclusively in children and adolescents. Since the use of mRNA-1273 was restricted in the youngest age groups due to the stronger association with

myocarditis, we were not able to provide reliable estimates for mRNA-1273 across all countries due to the rarity of the outcomes. Some older adolescents may have received an adenoviral vector vaccine, but given the rarity of many of the study outcomes, we were not able to provide reliable information on these vaccines, and we censored individuals receiving an adenoviral vector vaccine, a mRNA-1273 vaccine or a fourth dose of BNT. Vaccination was considered a time-varying exposure and individuals could contribute to follow-up both as unvaccinated and vaccinated. Among the vaccinated, we further stratified by the specific vaccination schedule. We used the nomenclature of BNTx for a BNT162b2 vaccine given as dose number x. We were able to evaluate the safety of the following homologous schedules: BNT1, BNT1BNT2, and BNT1BNT2BNT3. The 3-dose schedules were only relevant for adolescent 16-to-19-year olds and risk groups.

EXPOSURE VARIABLES - VACCINATION				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**
Vaccination schedule	Denmark	*The Danish Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.	Categorical (multiple levels): BNT1, BNT1BNT2, BNT1BNT2BNT3	Yes
	Finland	*The National Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.		
	Norway	*The Norwegian Immunisation Registry (SYSVAK).* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations		
	Sweden	*The National Vaccination Register.* Defined according to the type of COVID-19 vaccines administered and dates of vaccinations.		

Infection

The secondary exposure of interest was COVID-19 infection. To support risk/benefit evaluations, we provided comparable estimates of the associations between COVID-19 infection and the outcomes under study. In the secondary objectives on the risk of study outcomes following infection, we used a positive RT-PCR test as exposure. We included the first positive RT-PCR results for each individual from 1 January 2021 to 31 December 2022. We considered infection as a time-varying variable. The acute periods of interest started on day 1 (the day after a positive RT-PCR test) and lasted up to and including day 28 or 180 corresponding to risk period lengths of 28-days or 180-days. COVID-19 vaccinations and reinfections in the study period were considered censoring events.

EXPOSURE VARIABLES - INFECTION				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES**	**TIME-VARYING VARIABLE**
Documented SARS-CoV-2 infection	Denmark	The Danish Microbiology Database. Defined as the date of a positive PCR test for SARS-CoV-2.	Binary: yes/no	Yes
	Finland	National Infectious Diseases Register. Defined as the date of a positive PCR test.		
	Norway	Norwegian Surveillance System for Communicable Diseases (MSIS). Defined as the date of a positive PCR test or positive serology test for SARS-CoV-2.		
	Sweden	Register on surveillance of notifiable communicable diseases (SmiNet). Defined as the date of a positive PCR test for SARS-CoV-2.		

Study outcomes

We identified study outcomes using nationwide hospital registers: National Patient Registry (DK), National Care Register for Health Care (FI), the Norwegian Patient

Registry (NO) and the Swedish National Inpatient Register (SE). In the Nordic countries, serious diseases are diagnosed in the specialist care and hospital setting, often in specialised departments, and captured in our hospital contact registers used in our study if it is diagnosed. We included the following study outcomes identified in the national hospitalisation registers based on ICD-10 codes.

Study outcome	**ICD-10 codes used to identify cases**	
	ICD-10 codes with exactly 3-digits	ICD-10 codes with 4-digits
Autoimmune hepatitis		K754
Juvenile rheumatoid arthritis	M08	M080, M082, M083, M084, -M088, M089
Guillain-Barré syndrome		G610
Multiple sclerosis	G35	G359
Type 1 diabetes	E10	E100, E101, E102, E103, E104, E105, E106, E107, E108, E109

Identification of new-onset and flares of immune-mediated diseases

New onset of disease - We utilised a look-back period to identify new onset/incident cases defined as the first occurrence in the study period of a diagnosis without preceding occurrences in the 2-year period 1 January 2019 – 31 December 2020.

Flares - In the evaluations of flares, in contrast to new onset, we utilised a wash-out period with duration of 30 days following a hospital visit. Thus, three recordings of hospital visits in 90 days with 30 days between them were counted as one case in the new onset analyses and three hospital visits in the flare's analyses. It is notable, that for many immune-mediated diseases, 'flares' as defined above do not necessarily represent separate waves of disease activity, but might together be markers of disease-activity waves lasting for weeks or months or constitute routine check-ups.

Many of the diagnoses have been validated in the Nordic registers.[23] As an example, in Denmark, a type 1 diabetes diagnosis in the National patient registry was associated with a positive predictive value of 96% and completeness of 91%.[23]

Covariates

We took the following potential confounders into account: age, sex, year and calendar month, country-specific region, maternal country of birth (Nordic, Western, non-Western), comorbidities and vaccination priority group. The vaccination priority grouping was used to identify children given priority vaccination due to being at higher risk of severe COVID-19 outcomes. We used the Nordic hospitalisation register data to define individuals' comorbidities relevant to the outcomes under study.

COVARIATES				
VARIABLE	**COUNTRY**	**DATA SOURCE AND DETAILS**	**VALUES/CODES (ICD-10 codes for comorbidities specified with 3-digits should include all codes starting with the 3-digits)**	**TIME-VARYING VARIABLE**
Age	Denmark	*The Civil Registration System.* Defined as age during follow-up.	Categorical (3 levels): 5 to 11, 12 to 15, 16 to 19.	Yes (within a calendar year the age of a child is calculated as calendar year minus birth year). In descriptive table age is 2021 minus birth year. Children born in 2017 (4-year olds in 2021) that only contribute risk time in 2022 are listed as
	Finland	*The Finnish Population Information System.* Defined as age during follow-up.		
	Norway	*Norwegian Population Register.* Defined as age during follow-up.		
	Sweden	*The Total Population Register.* Defined as age during follow-up.		

				5-11-year olds.
Sex	Denmark	*The Civil Registration System.* Defined as biological sex at birth.	Binary: male, female	No
	Finland	*The Finnish Population Information System.* Defined as biological sex at birth.		
	Norway	*Norwegian Population Register.* Defined as biological sex at birth.		
	Sweden	*The Total Population Register.* Defined as biological sex at birth.		
Calendar year and month	Denmark	Defined as calendar month during follow-up.	Categorical (multiple levels): Jan-Mar 2021, Apr-Jun 2021, Jul-Sep 2021, Oct-Dec 2021, Jan-Mar 2022, Apr-Jun 2022, Jul-Sep 2022, Oct 2022.	Yes
	Finland	Defined as calendar month during follow-up.		
	Norway	Defined as calendar year and month during follow-up.		
	Sweden	Defined as calendar month during follow-up.		
Country specific region	Denmark	*The Civil Registration System.* Defined by the place of residence - major administrative regions.	Categorical (5 levels): Capital, Zealand, Southern Denmark, Central Jutland, Northern Jutland	No
	Finland	*The Finnish Population Information System.* Defined by the place of residence - major administrative regions.	Hospital districts: Helsinki and Uusimaa, Tampere, Turku, Oulu, and Other	
	Norway	*Norwegian Population Register.* Defined by the place of residence - Health administrative regions (4 categories)	Regions (4 categories): North, Central, West and South Eastern Norway Regional Health Authority.	
	Sweden	*The Total Population Register.* Defined by the place of residence - major administrative regions.	Categories are based on city size and urban vs rural.	

Maternal country of birth	Denmark	*The Civil Registration System.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, and non-Western	No
	Finland	*The Finnish Population Information System.* Defined as the place of birth of a child´s mother.	NA	
	Norway	*Norwegian Population Register.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, and non-Western	
	Sweden	*The Total Population Register.* Defined as the place of birth of a child´s mother.	Categorical (3 levels): Nordic, Western, and non-Western	
Comorbidity 1: Asthma	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	Yes
	Finland	*Care register for Health Care.*Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: J45-46	
Comorbidity 2: Other chronic respiratory diseases	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27	
	Norway	*Norwegian Patient Registry.*	Binary: yes/no	

		Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	ICD-10 codes: E84, J41-44, J47, J84, P27	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination. *Swedish Prescribed Drug Register.* Antidiabetic drugs use is defined as ≥2 filled prescriptions during 2020	Binary: yes/no ICD-10 codes: E84, J41-44, J47, J84, P27	
Comorbidity 3: Chronic cardiac disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	
	Sweden	*National Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: I05-08, I20-28, I34-37, I42-49, I50-51	
Comorbidity 4: Renal disease	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	

	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: N03, N05, N07, N18, N19, N25-27	
Comorbidity 5: Epilepsy or convulsions	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes / no ICD-10 codes: G40, R56	
Comorbidity 8: Congenital malformations and chromosomal abnormalities	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists	Binary: yes/no ICD-10 codes:	

		and before the first COVID-19 vaccination.	Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Q00-07, Q20-28, Q30-34, Q60-64, Q90-99	
Comorbidity 7: Malignancy or immunodeficiency	Denmark	*The National Patient Register.* Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	Yes
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	
	Sweden	*National Patient Register and Cancer register.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact and before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: C00-96, D70-72, D730, D81-84	
Comorbidity 8: Psychiatric disorder	*Denmark*	*The National Patient Register.* *Defined as primary diagnoses regardless of the type of hospital contact registered before the first COVID-19 vaccination.*	Binary: yes/no ICD-10 codes: Any chapter F diagnosis	*Yes*
	Finland	*Care register for Health Care.* Defined as primary or secondary diagnoses registered before the first COVID-19 vaccination.	Binary: yes/no ICD-10 codes: Any chapter F diagnosis	
	Norway	*Norwegian Patient Registry.* Defined as any recorded ICD-10 diagnosis during inpatient or outpatient contact in the hospital or from private-practising specialists and before the first COVID-19 vaccination.	Binary: yes/no Any chapter F diagnosis	
	Sweden	*National Patient Register.* Defined as any recorded ICD-10 diagnosis during inpatient or	Binary: yes/no ICD-10 codes:	

		outpatient contact and before the first COVID-19 vaccination.	Any chapter F diagnosis	
High-risk group	Denmark	A high-risk group variable was available (defined by comorbidities). In addition, we added nursing home status (everyone in a nursing home is considered high-risk, and there were a few children residing in nursing homes).	Binary: yes/no	Yes
	Finland	The high-risk group was taken as those in COVID-19 vaccination priority group 1, as described earlier.[24]	Binary: yes/no	
	Norway	A high-risk group variable was available (defined by comorbidities). In addition, we added nursing home status (everyone in a nursing home is considered high-risk, and there were a few children residing in nursing homes).	Binary: yes/no	
	Sweden	Vaccination before age-specific approval of use was considered vaccination of high-risk group children and adolescents. The dates were: 16+ – 21/12/2020, 12-15 yo – 28/05/2021, 5-11 yo – 25/11/2021.	Binary: yes/no	

9.5 Data Sources

We used the unique nationwide register data to construct country-specific cohorts with individual-level information on dates of vaccination and dates of outcomes together with relevant covariate information. All Nordic residents are assigned a unique national personal identifier at birth or immigration, enabling unambiguous linkage between registers within each country. The registers were updated daily and there was minimal lag time (except for the Swedish and Finnish patient registers, for which there was a lag of 2 to 4 weeks); we did not expect the lag time of information from these data sources to differentiate between vaccinated and unvaccinated groups. The Nordic countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, which provided near-complete follow-up of the study population over time.

In the following tables, we present the key data sources (vaccinations, RT-PCR positive tests and hospital contacts) for our study. All data sources were nationwide registers. All study subcontractors had access to their country-specific data and could link data between registers for our study.

Country	**Details of the individual-level data sources**						
Denmark							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
The Danish vaccination register	The register holds information on all vaccinations given in Denmark including information on vaccination date, type, dose, and product batch number ever since November 15, 2015 (when reporting to the register became mandatory).	Register	Nationwide	2020 – today	Daily	No lag	[25]
The National patient registry	The register covers all hospital contacts/visits in Denmark with information on the duration of the contact/visit, department of admission and other hospital characteristics. Treating physician-assigned diagnoses have been registered according to ICD-10 codes since 1995.	Register	Nationwide	1995 - today	Daily	No lag	[26]
The Danish Microbiology Database	Information on positive results of RT-PCR tests for SARS-CoV-2 are obtained from The Danish Microbiology Database (MiBa) which holds information on all microbiology samples analysed at Danish departments of microbiology, including information on SARS-CoV-2 PCR test results, date of sampling, date of analysis, type of test and interpretation of the test (positive / negative). The SARS-CoV-2 PCR tests have been freely available to all individuals in Denmark regardless of symptom status throughout the COVID-19 pandemic.	Register	Nationwide	2020 – today	Daily	No lag	[27]

Country	Details of the individual-level data sources						
Finland							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
The National Vaccination Register	The register, which is based on the Register of Primary Health Care Visits, holds information on all COVID-19 vaccinations administered in Finland. Data include the date of vaccination, vaccine batch number and trade name.	Register	Nationwide	2020 - today	Daily	No lag	[28]
National Care Register for Health Care	The register comprises information on all in-hospital care (since 1969) and outpatient specialist care (since 1998) in Finland, including admission and discharge dates, whether hospitalization was planned or acute, codes for discharge diagnoses (according to ICD-10) and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department and hospital. The register is held by the Finnish Institute for Health and Welfare.	Register	Nationwide	2005 - today	Daily	1-4 weeks	[29]
Finnish National Infectious Diseases Register	The register contains information on notifiable diseases which must be reported by the laboratories and the physician treating the patient, or performing an autopsy, in accordance with the Finnish Communicable Diseases Act. All laboratory-confirmed SARS-CoV-2 infections are recorded in the National Infectious Diseases Register The register is held by the Finnish Institute for Health and Welfare.	Register	Nationwide	2020 - today	Daily	0-1 weeks	[30]

Country	Details of the individual-level data sources						
Norway							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
The Norwegian immunisation register (SYSVAK)	The register holds information on administered vaccines in the Norwegian vaccination programs, including the date of administration and type of vaccine. For the COVID-19 vaccines, reporting to the register has been mandatory.	Register	Nationwide	2020 - today	Daily	No lag	[31]
The Norwegian Patient Registry (NPR)	The register holds information on all contacts with specialist health-care services in Norway, including admission and discharge dates as well as diagnoses (recorded according to ICD-10) during hospitalization or outpatient contact.	Register	Nationwide	2017 - today	Daily	No lag	[32]

Norwegian Surveillance System for Communicable Diseases (MSIS)	The register holds information on selected infectious diseases for which reporting to the register is mandatory. This includes all COVID-19 tests and the date of testing and test results.	Register	Nationwide	2020 - today	Daily	No lag	[33]

Country	**Details of the individual-level data sources**						
Sweden							
Title	**Info**	**Type**	**Setting**	**Study availability**	**Update**	**Lag**	**Ref**
Swedish vaccination register	The register contains information on administered COVID-19 vaccines including data on the date of administration, the specific vaccine products, substance, formulation, batch number and dose number (for repeated doses) since 1 January 2021. The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2020 - today	Daily	No lag	[34]
Swedish national inpatient register	The register comprises information on all in-hospital (since 1987) and out-patient (since 2001) specialist care in Sweden including data on admission and discharge dates, whether hospitalization was planned or acute, codes for discharge diagnoses and surgical procedures, whether discharged as deceased, to own private residence or other health care facilities, type of department, and hospital. For the current study period discharge diagnoses were recorded according to the Swedish clinical modification of the ICD-10 (i.e. ICD-10-SE). The register is held by the National Board of Health and Welfare.	Register	Nationwide	2017 - today	Monthly	2–4 week	[35]
Register on Surveillance Of Notifiable Communicable Diseases (Sminet)	The register contains information on notifiable diseases (for which reporting is mandatory) reported by either the analysis-performing laboratories, the treating physician or the autopsy-performing physician, in accordance with the Swedish Communicable Diseases Act. Data include the date of disease occurrence, date of testing, date of positive test and diagnoses. The register is held by the Public Health Agency of Sweden.	Register	Nationwide	2020 - today	Daily	No lag	[36]

9.6 Bias and limitations

The use of Nordic nationwide registers mitigates concern for potential selection bias and recall bias in our study since the complete populations are included and since exposures

and outcomes are assessed independently. Furthermore, the use of complementary statistical approaches reduces concerns about confounding. The SCCS approach eliminates time-independent confounding due to factors such as genetics, socio-demographics and lifestyle by design, while the contemporary cohort analysis have fewer statistical assumptions including the assumption of event-dependent exposure in the SCCS approach. Nonetheless, a number of limitations should be mentioned particularly related to the study of immune-mediated diseases.

Diagnostic lag

The national hospital registers do not have information on date of symptom onset, only the date of diagnosis, and therefore we must expect a lag between onset of symptoms and diagnosis. This is a particular issue with diseases with an insidious onset and should be considered carefully in the interpretation of results. An association, especially in the short-term risk period, may not be causal, but could be a result of unmasking of a subclinical pre-existing condition. Unmasking occurs when health-care contacts where a vaccine is administered also initiates diagnostic workup which leads to unmasking of conditions that would otherwise have progressed further before diagnosis.[23]

Definition of flares

In this study, disease flares were defined by recurrent hospital visits. However, we cannot expect that a hospital visits in itself constitutes a disease flare it may also be a routine visit. Many patients with immune-mediated diseases have regular check-ups at the hospital. In register-data, we cannot distinguish between the purpose of the visit. An increase in hospital visits due to disease flares can be detected under the condition that regular check-ups are not too frequent. If check-ups are frequent, a disease flare may not manifest as additional visits. If check-ups are less frequent, a disease flare manifesting as one or more visits can be detected if statistical power is sufficient. In the current study we utilise a wash-out period of 30-days, since hospital visit recordings over shorter periods are more likely to be related to the same clinical event. As an example, 3 hospital visit recordings in 5 days, are more likely due to visiting different hospital departments, than separate clinical events.

Main periods of risk

In this study we compare the incidence rate in a main risk period after vaccination to the rate during unvaccinated follow-up. Temporality is a key criterion in establishing causality. Utilising a main risk period following vaccination facilitates the detection of true associations. We have included separate analyses of both a shorter- and a longer-term main risk period (i.e. 28- and 180-days) to be able to identify associations for immediate onset outcomes and insidious onset outcomes.

Rarity of outcomes

New onset of immune-mediated diseases in children and adolescents are fortunately rare events. This is particularly the case for autoimmune hepatitis and Guillain-Barré syndrome which are included in our study. Even in a setting with nationwide data from multiple countries, the statistical precision in our estimates will be limited.

Long-term outcomes

The duration of follow-up is limited by the recency of the vaccination campaigns in children and adolescents in the Nordic countries. The calendar period of vaccination depends on the age, but most study participants will not have much follow-up beyond 12 months, and, thus, associations with immune-mediated diseases manifesting with onset beyond 12 months will not be detected in the current study.

Comparability of vaccinated and unvaccinated

When vaccination uptake is too high or too low, the comparability of vaccinated and unvaccinated is affected by selection bias. In the Nordic setting, uptake of at least one dose of BNT was high e.g. 75.5% in Denmark and 71.5% in Sweden among 12-to-15-year-olds (section 9.7 below). However, among 5-11-year olds, the uptake was lower, ranging from 1.5% in Norway to 39.3% in Denmark (section 9.7 below). In in countries without a general recommendation for this age group, vaccinated individuals are more likely to have been from risk groups predisposing to severe disease. This is also the case for BNT1BNT2BNT3 exposed individuals.

Exposure ascertainment - infection

Our ascertainment of SARS-CoV-2 infection was based on secondary use of national microbiology test results. Depending on the country and period, we did not have complete registration of all infected children and adolescents in the population, only those who tested positive. However, in more than half of the study period we expect the number of unrecognized infections in the Nordic setting to be low-to-moderate given the extensive testing regimes that were in place until the end of February 2022.

Exposure ascertainment - vaccination

Given the preferential use of BNT162b2 in younger age groups, we were not able to provide reliable safety information on the mRNA-1273 vaccine or any other vaccine type approved by EMA for these particular age groups.

9.7 Study size (sample size and power)

Prior to study conduct, we expected the Nordic countries to contribute with a total population of 5.1 million children/adolescents. The following tables below shows the country-specific details on population size and expected COVID-19 vaccine uptake:

DENMARK (Status as of 22 November 2022)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	169786 (39.3%)	138267 (32.0%)	76 (0.0%)	0 (0.0%)	262071 (60.7%)
12 to 15 yrs	206869 (75.5%)	198170 (72.3%)	694 (0.3%)	53 (0.0%)	67069 (24.5%)
16 to 19 yrs	245739 (88.2%)	242447 (87.0%)	66238 (23.8%)	771 (0.3%)	32997 (11.8%)
Total 5 to 19 yrs	622394 (63.2%)	578884 (58.8%)	67008 (6.8%)	824 (0.1)	362137 (36.8%)

FINLAND (Status as of 27 September 2022)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	104,714 (24.9%)	57,193 (13.6%)	0 (0.0%)	0 (0.0%)	345,828 (82.2%)
12 to 17 yrs	283,595 (76.3%)	259,064 (69.7%)	14,495 (3.9%)	0 (0.0%)	88,090 (23.7%)
18 to 24 yrs	360,178 (84.9%)	339,814 (80.1%)	134,059 (31.6%)	1,696 (0.4%)	64,060 (15.1%)

Total **5 to 24 yrs**	748,487 (61.5%)	656,071 (53.9%)	148,554 (12.2%)	1,696 (0.14%)	497,978 (40.9%)

NORWAY (Status as of September 2022)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
5 to 11 yrs	6,137 (1.3%)	1,054 (0.2%)	7 (0%)	0	452,024 (98.4%)
12 to 15 yrs	127,957 (45.2%)	19,694 (6.9%)	167 (0.1%)	6 (0%)	135,297 (47.8%)
16 to 19 yrs	59,682 (21.9%)	132,617 (48.7%)	32,447 (11.9%)	108 (0.04%)	47,401 (17.4%)
Total **5 to 19 yrs**	193,776 (19.1%)	153,365 (15.1%)	32,621 (3.2%)	114 (0.01%)	634,722 (62.6%)

SWEDEN (Status as of August 22)	**1 dose**	**2 doses**	**3 doses**	**4 doses**	**Unvaccinated**
12 to 15 yrs	24,920 (5.0%)	328,492 (66.5%)	1,092 (0.2%)	7 (0.0%)	139,209 (28.2%)
16 to 19 yrs	18,904 (4.1%)	25,2671 (54.3%)	114,084 (24.5%)	525 (0.1%)	79,401 (17.1%)
Total **12 to 19 yrs**	43,824 (4.6%)	581,163 (60.6%)	115,176 (12.0%)	532 (0.1%)	218,610 (22.8%)

Among the European countries that have implemented childhood/adolescent COVID-19 vaccination, the uptake rates in the Nordic countries are in the higher end. The median

uptake in the European region among individuals 5 to 17 years of age was 23.3% (range from 2.1 to 44.7%) - https://www.ecdc.europa.eu/sites/default/files/documents/Overview-of-the-implementation-of-COVID-19-vaccination-strategies-and-deployment-plans-in-the-EU-EEA-April-2022.pdf .

The statistical power was determined by the observed incidence rates in our study and the uptake of vaccination. All our outcomes were rare events, and thus statistical precision was limited to some extent. However, since we had fully utilised all available nationwide data during the period where COVID-19 vaccination has been available to 5-to-19-year-olds in the Nordic country, the statistical power of the study was directly reflected in the resulting 95% confidence intervals of our estimates of associations.

9.8 Data management

Data management and statistical analyses were conducted using a Common Data Model (CDM), by which national register data were standardised to a common structure, format and terminology in order to allow the same statistical programming scripts to be used in each country. The use of a CDM with common statistical programming scripts facilitated efficient use of resources and reproducibility of the statistical analyses. This process was facilitated by the homogeneity of the registers used in the Nordic countries.

The CDM contained detailed descriptions of how the different data sources for the study were to be organised and how the different variables in the data sources were defined. The analytical group in Denmark coded the statistical analyses using R-scripts (R version 4.2.2.). The R-scripts were made available on GitHub (also during the programming phase to facilitate input and comments). The analysts in each of the participating countries then ran the R-scripts and returned the output to Denmark. The country-specific results were combined in meta-analyses in Denmark. We were not able to combine the country-specific data directly due to data privacy regulations and it was not feasible to negotiate the approval of data sharing between four countries in due time.

9.9 Statistical methods

Contemporary cohort analysis

In each Nordic country, we estimated adjusted incidence rate ratios and excess risks by comparing main risk period follow-up to unvaccinated follow-up. We used Poisson regression on the outcome counts with the logarithm of the follow-up time as the offset. We took potential confounders (described above) into account by direct adjustment (multivariable regression). Country-specific estimates were combined using meta-analyses; the combined incidence rate ratio estimates were based on random effects models implemented using the *mixmeta* package in R.

Self-controlled case series

The self-controlled case series (SCCS) were nested within the cohorts. The SCCS analyses compared periods of follow-up within cases only. We included both vaccinated and unvaccinated cases. While the unvaccinated cases do not inform on the association between exposure and outcome, they do provide information on any variables included for adjustment. All time-invariant confounders such as comorbidity and lifestyle factors were taken into account by design. In each Nordic country, we compared main risk period follow-up to the unvaccinated period to estimate incidence rate ratios using conditional Poisson regression with direct adjustment for calendar year and month. We used a 14-day pre-risk period before vaccination to take into account a potential healthy vaccinee effect. The pre-risk period of interest occurred before any dose. The pre-risk period was not included in the unvaccinated reference period. Being diagnosed with the outcome of interest was not a censoring criterion in the SCCS analyses, and follow-up was continued to allow for the possibility that an individual was later vaccinated. However, we only considered the first recording of a relevant immune-mediated disease diagnosis.

We combined country-specific results using the meta-analysis approach described above. The main assumption underlying the SCCS approach is that occurrence of the event under study (see section 'study outcomes') before exposure (vaccination) did not influence the future probability of exposure – so-called event-dependent exposure.

Hospital visits – flares analyses

In the flares analysis, each individual could contribute with multiple hospital visits during follow-up. The follow-up was not censored in the contemporary cohort analyses in the event of a relevant hospital visit occurring and we did not only consider the first recording of the immune-mediated disease diagnosis in the SCCS analyses.

Sensitivity analyses

We conducted sensitivity analyses where we stratified by age (5 to 11, 12 to 15, 16 to 19) and sex (male or female) for both the SCCS analyses and the contemporary cohort analyses.

Excess risks

Excess risks were calculated using the relative risk estimates from the contemporary cohort analyses.

9.10 Supplementary analyses and quality control

The use of two different statistical analyses approaches (SCCS and contemporary cohort analyses) constitutes our primary quality control. The strength and limitations of these approaches complement each other well. If the two methods yield similar results, this supports that validity of the results. We utilised a common data model for the Nordic register data together with standardised analysis scripts which further supports the quality of the statistical analyses.

10. RESULTS

10.1 Results – New Onset

10.1.1 Participants and Descriptive data

The total population under study was 5,029,084 5-to-19-year-olds (2,448,349 girls [49%] and 2,580,735 boys [51%]) from Denmark (n=1,035,158), Finland (n=1,018,113), Norway (n=1,094,157) and Sweden (n=1,881,656); Table 1.

The combined cohort comprised 2,387,657 individuals vaccinated at least once. The total number of BNT doses administered was 4,145,463 doses. The vaccine uptake of at least one COVID-19 vaccine at the study end on 31 December 2022 was highest in Denmark (65.3% of all 5-to-19-year-olds), followed by Finland (52.6%), Norway (40.1%) and Sweden (39.2%). Two doses of BNT was the most common schedule used in Denmark (50.2% of all 5-to-19-year-olds), Finland (28.0%), and Sweden (26.9%), while one dose of BNT was the most common schedule in Norway (17.8%). Only 14.5% of all 5-to-11-year-olds were vaccinated at least once, while the majority of 12-to-15-year-olds (74.5%) and 16-to-19-year-olds (85.1%) were vaccinated at least once. In the older age groups with higher uptakes, 51.4% of 12-to-15-year-olds and 43.6% of 16-to-19-year-olds received two doses of BNT. Three doses of BNT were almost exclusively used among 16-to-19-year-olds (22.2%). Uptake was similar across sexes, while children with comorbidities (n=541,563 [10.7%]) had higher uptake than children without comorbidities; Table 1.

The number of infected children (children with a positive RT-PCR test) at the study end on 31 December 2022 was largest in Denmark (n=734820, 71.0%), followed by Norway (n=464624 [42.5%]), Sweden (n=443004 [23.5%]), and Finland (n=217881 [21.4%]); Table 1. The proportion of infection was similar in girls (37.7%) and boys (36.3%), but slightly higher in 12-to-15-year-olds (39.9%) and 16-to-19-year-olds (39.5%) than in 5-to-11-year-olds (34.2%). Children with 2 or more comorbidities had slightly lower infection rates (33.6%) than children with 1 comorbidity (36.2%) or no comorbidity (37.1%); Table 1.

10.1.2 Outcome data

The incidence rates (per 100,000 person-years of follow-up) of all the study outcomes in the combined Nordic cohorts during the study period 1 January 2021 to 31 December 2022 are presented in Table 5 stratified by age-group (5-to-11-year-olds, 12-to-15-year-olds and 16-to-19-year-olds). Autoimmune hepatitis and Guillain-Barré syndrome were very rare with incidence rates of 1.1 and 0.6 per 100,000 person-years and type 1 diabetes was rare with an incidence rate of 41.5 per 100,000 person-years. Onsets of

Guillain-Barré syndrome and autoimmune hepatitis were most common in 16-to-19-year-olds, while type 1 diabetes incidence peaked among 12-to-15-year-olds.

10.1.3 Main results

Autoimmune hepatitis

In the evaluation of the 28-day main risk period (Table 2), we observed no statistically significant associations between any dose of BNT or infection and autoimmune hepatitis. Cases were few among exposed participants, and not all countries were able to produce estimates for the meta-analysis. Only the association with BNT1BNT2 was estimable among vaccinated, SCCS RR 0.71 (95% CI, 0.07-7.45) and contemporary cohort analysis RR 1.06 (0.13-8.77).

In the evaluation of the 180-day main risk period (Table 3), we observed no statistically significant associations between any dose of BNT or infection and autoimmune hepatitis. Cases were few among BNT1BNT2 and BNT1BNT2BNT3 exposed participants, and not all countries were able to contribute estimates for all associations. In the contemporary cohort analysis, we did observe an increased risk associated with BNT1BNT2BNT3, RR 4.97 (95% CI, 0.83-29.85). However, statistical precision was low and a similar association was not observed in the SCCS analysis, RR 0.73 (0.09-5.70). Sensitivity analyses revealed that the association was primarily borne out by girls, RR 14.74 (1.18-184.93); Table 4d.

Guillain-Barré syndrome

In the evaluation of the 28-day main risk period (Table 2), we observed no statistically significant associations between any dose of BNT and Guillain-Barré syndrome. No cases were observed after vaccination. In both the SCCS and the contemporary cohort analyses, we observed strong, but imprecise, associations, between infection and Guillain-Barré syndrome, SCCS RR 52.84 (95% CI, 5.70-489.40) and contemporary cohort analysis RR 15.10 (1.11-205.94). In sensitivity analyses, the association appeared to be most marked among 5-to-11-year-olds, SCCS RR 48.53 (2.60-905.30) (Table 4a), and girls, contemporary cohort analysis RR 57.37 (8.93-368.40) (Table 4c).

In the evaluation of the 180-day main risk period (Table 3), we observed an association between BNT1BNT2BNT3 and Guillain-Barré syndrome in the contemporary cohort analysis but not in the SCSS analysis, contemporary cohort analysis RR 20.93 (1.02-431.13) and SCCS RR was not estimable. Sensitivity analyses were not able to provide further insight due to too few cases; Table 4d. The association with infection was still present, SCCS RR 18.87 (95% CI, 1.60-223.04) and contemporary cohort analysis RR 3.85 (1.33-11.14). In sensitivity analyses of the SCCS analyses, the association

appeared to be most marked among 5-to-11-year-olds, SCCS RR 38.76 (1.33-1131.97) (Table 4b). In sensitivity analyses of the contemporary cohort analyses, the association appeared to be most marked in girls, contemporary cohort analysis RR 7.96 (2.28-27.79), and 12-to-15-year-olds, RR 6.64 (0.68-64.96) (Table 4d).

Type 1 diabetes

In the evaluation of the 28-day main risk period (Table 2), we observed no statistically significant increased risks between any dose of BNT and type 1 diabetes. There was a protective effect of BNT1BNT2 in the SCCS analyses, RR 0.66 (95% CI, 0.46-0.95), but not in the contemporary cohort analysis, RR 1.01 (0.76-1.35), and the confidence interval was compatible with no clinically meaningful effect. In both the SCCS analyses and the contemporary cohort analyses, risk of type 1 diabetes was increased after infection, but confidence intervals were compatible with small to no clinically meaningful effects. In sensitivity analyses, the association appeared to be most marked in 16-to-19-year-olds, SCCS RR 3.78 (1.43-9.99) (Table 4a) and contemporary cohort analysis RR 2.74 (1.33-5.63) (Table 4c).

In the evaluation of the 180-day main risk period (Table 3), we observed no statistically significantly increased risk following any dose of BNT or infection and type 1 diabetes. Notably, all countries were able to contribute to all meta-analysed associations.

10.1.4 Other analyses

In Tables 6 and 7, we present the excess risks of the study outcomes according to age group based on the relative risks from the contemporary cohort analyses for the 28-day and the 180-day main risk periods, respectively.

In 5-to-11-year-olds, the association between infection and Guillain-Barré syndrome in the 28-day main risk period corresponded to an excess risk of 2.68 cases per 100,000 infections (95% CI, 2.27-2.75). In the 180-day main risk period, the association corresponded to an excess risk of 0.14 cases per 100,000 infections (95% CI, 0.05-0.17).

10.2 Results – Flares

10.2.1 Participants and Descriptive data

Juvenile rheumatoid arthritis patients

We included 8680 juvenile rheumatoid arthritis patients (Table 8). Vaccination uptake was high across countries in this patient population, 72.9%. Sweden had the highest uptake in this patient population (81.5%), followed by Denmark (76.7%), Finland (68.8%) and Norway (64.3%). BNT1BNT2 was the most common schedule across countries (41.2% of all patients). The 16-to-19-year-olds had the highest uptake (89.6%) followed by the 12-to-15-year-olds (79.8%) and the 5-to-11-year-olds (34.5%). There were only small differences between girls and boys, and additional comorbidities in this patient population was associated with higher uptake of BNT1BNT2BNT3 than no comorbidities (22.4% vs 14.0%).

Multiple sclerosis patients

We were only able to include 162 multiple sclerosis patients (Table 8). Vaccination uptake was high across countries, 83.3%. The most common schedule across countries were BNT1BNT2BNT3 (35.8%).

Type 1 diabetes patients

We included 18905 type 1 diabetes patients (Table 8). Vaccination uptake was high across countries, 77.6%. Sweden had the highest uptake in this patient population (84.6%), followed by Denmark (81.9%), Finland (76.2%) and Norway (65.5%). BNT1BNT2 was the most common schedule across countries (43.3% of all patients). The 16-to-19-year-olds had the highest uptake (90.5%) followed by the 12-to-15-year-olds (82.7%) and the 5-to-11-year-olds (37.6%). There were only small differences between girls and boys, and additional comorbidities in this patient population was associated with higher uptake of BNT1BNT2BNT3 than no comorbidities (21.8% vs 16.5%).

10.2.2 Outcome data

The incidence rates (per person-year of follow-up) of hospital visits in the three patient cohorts during the study period 1 January 2021 to 31 December 2022 are presented in Table 12 stratified by age-group (5-to-11-year-olds, 12-to-15-year-olds and 16-to-19-year-olds). The rate of visits was highest among type 1 diabetes and multiple sclerosis patients (4.4 and 4.4 per person-year, respectively). For all patient cohorts, the younger age groups had more visits than older age groups; Table 12.

In the vast majority of cases, hospital visits were in the context of outpatient contacts (Figure 1). For all three patient cohorts, the most common number of outpatient visits during the 2-year study period, was 3; Figure 1. Boxplots of the number of visits per patient stratified according to country and inpatient/outpatient is presented in Figure 2.

10.2.3 Main results

Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients

In the evaluation of the 28-day main risk period (Table 9), we observed no statistically significant associations between any dose of BNT or infection and hospital visits related to juvenile rheumatoid arthritis. All countries contributed to all analyses.

In the evaluation of the 180-day main risk period (Table 10), we observed an increase in the risk of visits after BNT1 in the contemporary cohort analysis, RR 1.09 (95% CI, 1.03-1.16), but not in the SCCS analysis, RR 1.05 (0.96-1.14). The sensitivity analyses did not provide any further insights on association (Table 11d).

Multiple sclerosis visits among multiple sclerosis patients

In the evaluation of the 28-day main risk period (Table 9), we observed no statistically significant associations between any dose of BNT or infection and hospital visits related to multiple sclerosis. It should be noted that we did observe associations for all BNT schedules and multiple sclerosis visits in boys in both the contemporary cohort analysis and in the SCCS analysis (Table 11a and Table 11c). The association was strongest for BNT1BNT2BNT3 where we observed a SCCS RR of 15.01 (95% CI, 1.78-126.82) and a contemporary cohort analysis RR of 22.93 (5.22-100.83).

In the evaluation of the 180-day main risk period (Table 10), we observed no statistically significant increased risks between any dose of BNT or infection and hospital visits related to multiple sclerosis. However, a reduced risk of visits after BNT1BNT2BNT3 was observed in both the SCCS analysis, RR 0.33 (95% CI, 0.15-0.71), and the contemporary cohort analyses, RR 0.46 (0.23-0.92). The sensitivity analyses did not provide any further insights on association (Tables 11b and 11d).

Type 1 diabetes visits among type 1 diabetes patients

In the evaluation of the 28-day main risk period (Table 9), we observed an increase in visits related to type 1 diabetes after BNT1BNT2 in the SCCS analysis, RR 1.09 (95% CI, 1.04-1.14), but not in the contemporary cohort analysis, RR 1.04 (0.97-1.11). The sensitivity analyses (Table 11a) suggested that this was an association primarily borne out in the 12-to-15-year olds (RR 1.10, 0.96-1.49) and the 16-to-19-year-olds (RR 1.18, 1.05-1.32). All countries contributed to all analyses.

In the evaluation of the 180-day main risk period (Table 10), we observed slight increases in the risk of visits after BNT1 and BNT1BNT2 in the SCCS analysis, RR 1.10 (1.02-1.18) and RR 1.05 (1.01-1.10). This was not observed in the contemporary cohort analyses. The sensitivity analyses (Table 11b) suggested that this was an association primarily borne out in the 12-to-15-year olds (e.g. RR 1.22, 1.06-1.41, for BNT1BNT2) and the 16-to-19-year-olds (RR 1.17, 1.03-1.34, for BNT1BNT2). All countries contributed to all analyses.

10.2.4 Other analyses

In Tables 13 and 14, we present the excess number of hospital visits per 1000 vaccinations/infections according to age group based on the relative risks from the contemporary cohort analyses for the 28-day and the 180-day main risk periods, respectively.

10.3 Figures and tables

Table 1: Vaccination and infection status at study end among 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden

Characteristic	Unvaccinated N (%[1])	BNT1 N (%[1])	BNT1BNT2 N (%[1])	BNT1BNT2BNT3 N (%[1])	Other N (%[1])	Infected N (%[1])	Non-infected N (%[1])	Total
Denmark	359368 (34.7%)	43871 (4.2%)	520084 (50.2%)	107111 (10.3%)	4724 (0.5%)	734820 (71.0%)	300338 (29.0%)	1035158
Finland	482799 (47.4%)	75767 (7.4%)	285183 (28.0%)	47318 (4.6%)	127046 (12.5%)	217881 (21.4%)	800232 (78.6%)	1018113
Norway	655277 (59.9%)	194788 (17.8%)	153910 (14.1%)	39322 (3.6%)	50860 (4.6%)	464624 (42.5%)	629533 (57.5%)	1094157
Sweden	1143983 (60.8%)	41047 (2.2%)	506203 (26.9%)	92659 (4.9%)	97764 (5.2%)	443004 (23.5%)	1438652 (76.5%)	1881656
Girls	1270115 (51.9%)	168159 (6.9%)	710475 (29.0%)	154220 (6.3%)	145380 (5.9%)	922512 (37.7%)	1525837 (62.3%)	2448349
Boys	1371312 (53.1%)	187314 (7.3%)	754905 (29.3%)	132190 (5.1%)	135014 (5.2%)	937817 (36.3%)	1642918 (63.7%)	2580735
Age 5 to 11	2125032 (85.5%)	104621 (4.2%)	256190 (10.3%)	574 (0.0%)	393 (0.0%)	851578 (34.2%)	1635232 (65.8%)	2486810
Age 12 to 15	330119 (25.5%)	202600 (15.7%)	665158 (51.4%)	8163 (0.6%)	87477 (6.8%)	515831 (39.9%)	777686 (60.1%)	1293517
Age 16 to 19	186276 (14.9%)	48252 (3.9%)	544032 (43.6%)	277673 (22.2%)	192524 (15.4%)	492920 (39.5%)	755837 (60.5%)	1248757
0 comorbidity	2447988 (54.6%)	311103 (6.9%)	1258973 (28.1%)	236058 (5.3%)	233399 (5.2%)	1665670 (37.1%)	2821851 (62.9%)	4487521
1 comorbidity	171461 (35.8%)	39064 (8.2%)	183437 (38.3%)	43310 (9.0%)	41762 (8.7%)	173629 (36.2%)	305405 (63.8%)	479034
2+ comorbidities	21978 (35.1%)	5306 (8.5%)	22970 (36.7%)	7042 (11.3%)	5233 (8.4%)	21030 (33.6%)	41499 (66.4%)	62529
Total	2641427 (52.5%)	355473 (7.1%)	1465380 (29.1%)	286410 (5.7%)	280394 (5.6%)	1860329 (37.0%)	3168755 (63.0%)	5029084

[1]Row percentages.

Table 2: Relative risks of onset of immune-mediated diseases in the 28 day risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	SCCS analysis		Contemporary cohort analysis		
Exposure	**Number of cases**	**Relative Risk (95% CI)**	**Number of cases**	**Relative Risk (95% CI)**	**Countries included in analyses**
Autoimmune hepatitis					
Unvaccinated	54	1 (ref)	54	1 (ref)	-
BNT1	0	NA	0	NA	NA
BNT1BNT2	<5	0.71 (0.07-7.45)	<5	1.06 (0.13-8.77)	SE
BNT1BNT2BNT3	0	NA	0	NA	NA
Non-infected	54	1 (ref)	54	1 (ref)	-
SARS-CoV-2 infection	<5	1.02 (0.09-11.56)	<5	4.58 (0.52-40.40)	NO
Guillain-Barré syndrome					
Unvaccinated	31	1 (ref)	31	1 (ref)	-
BNT1	0	NA	0	NA	NA
BNT1BNT2	0	NA	0	NA	NA
BNT1BNT2BNT3	0	NA	0	NA	NA
Non-infected	30	1 (ref)	31	1 (ref)	-
SARS-CoV-2 infection	<5	52.84 (5.70-489.40)	<5	15.10 (1.11-205.94)	DK, FI
Type 1 diabetes					
Unvaccinated	2112	1 (ref)	2157	1 (ref)	-
BNT1	80	0.81 (0.62-1.05)	80	1.10 (0.87-1.39)	DK, FI, SE, NO
BNT1BNT2	51	0.66 (0.46-0.95)	51	1.01 (0.76-1.35)	DK, FI, SE, NO
BNT1BNT2BNT3	<5	0.49 (0.12-2.10)	<5	1.00 (0.24-4.06)	DK, SE
Non-infected	2132	1 (ref)	2158	1 (ref)	-
SARS-CoV-2 infection	41	1.29 (0.91-1.82)	41	1.31 (0.95-1.80)	DK, FI, SE, NO

Table 3: Relative risks of onset of immune-mediated diseases in the 180 day risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	SCCS analysis		Contemporary cohort analysis		
Exposure	**Number of cases**	**Relative Risk (95% CI)**	**Number of cases**	**Relative Risk (95% CI)**	**Countries included in analyses[1]**
Autoimmune hepatitis					
Unvaccinated	54	1 (ref)	54	1 (ref)	-
BNT1	12	0.67 (0.25-1.78)	12	0.83 (0.37-1.86)	DK, SE, NO
BNT1BNT2	<5	0.41 (0.03-5.00)	<5	1.04 (0.12-9.36)	SE
BNT1BNT2BNT3	<5	0.73 (0.09-5.70)	<5	4.97 (0.83-29.85)	DK, FI[1], SE
Non-infected	54	1 (ref)	54	1 (ref)	-
SARS-CoV-2 infection	<5	0.43 (0.07-2.57)	6	2.38 (0.87-6.56)	DK[1], FI, NO
Guillain-Barré syndrome					
Unvaccinated	31	1 (ref)	31	1 (ref)	-
BNT1	6	1.28 (0.27-6.17)	6	1.31 (0.38-4.51)	DK, SE, NO
BNT1BNT2	0	NA	0	NA	NA
BNT1BNT2BNT3	0	NA	<5	20.93 (1.02-431.13)	NO
Non-infected	30	1 (ref)	31	1 (ref)	-
SARS-CoV-2 infection	6	18.87 (1.60-223.04)	8	3.85 (1.33-11.14)	DK, FI, SE[1], NO[1]
Type 1 diabetes					
Unvaccinated	2112	1 (ref)	2157	1 (ref)	-
BNT1	433	0.74 (0.59-0.94)	433	1.11 (0.97-1.28)	DK, FI, SE, NO
BNT1BNT2	70	0.57 (0.39-0.83)	70	1.12 (0.75-1.69)	DK, FI, SE, NO
BNT1BNT2BNT3	20	0.48 (0.28-0.81)	20	1.30 (0.82-2.07)	DK, FI, SE, NO
Non-infected	2132	1 (ref)	2158	1 (ref)	-
SARS-CoV-2 infection	189	0.92 (0.73-1.15)	189	0.94 (0.80-1.11)	DK, FI, SE, NO

[1]Indicates that this specific country is not included across all analysis methods.

Table 4a: Sensitivity analyses of the SCCS relative risks of onset of immune-mediated diseases in the 28 day main risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Autoimmune hepatitis					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA
BNT1BNT2	NA	1.45 (0.10-20.83)	NA	NA	0.44 (0.02-9.49)
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	NA	NA	NA	2.19 (0.09-52.82)
Guillain-Barré syndrome					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA
BNT1BNT2	NA	NA	NA	NA	NA
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	NA	48.53 (2.60-905.30)	NA	NA
Type 1 diabetes					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.98 (0.73-1.32)	0.58 (0.31-1.08)	0.55 (0.17-1.74)	0.94 (0.61-1.44)	1.26 (0.81-1.97)
BNT1BNT2	0.74 (0.50-1.12)	0.57 (0.35-0.93)	0.34 (0.10-1.11)	0.58 (0.34-0.98)	1.16 (0.69-1.94)
BNT1BNT2BNT3	0.97 (0.12-7.67)	2.55 (0.25-26.20)	NA	NA	0.83 (0.17-3.97)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.21 (0.71-2.06)	1.42 (0.52-3.89)	1.05 (0.57-1.92)	1.47 (0.66-3.29)	3.78 (1.43-9.99)

Table 4b: Sensitivity analyses of the SCCS relative risks of onset of immune-mediated diseases in the 180 day main risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Autoimmune hepatitis					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.36 (0.04-2.97)	1.15 (0.21-6.13)	NA	0.93 (0.07-11.92)	0.39 (0.10-1.53)
BNT1BNT2	0.27 (0.01-5.19)	NA	NA	NA	0.16 (0.01-4.32)
BNT1BNT2BNT3	NA	3.37 (0.10-118.05)	NA	NA	0.44 (0.02-8.03)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	0.55 (0.03-8.94)	NA	NA	0.93 (0.02-37.38)
Guillain-Barré syndrome					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.87 (0.10-7.72)	NA	NA	8.15 (0.05-1251.28)	NA
BNT1BNT2	NA	NA	NA	NA	NA
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	NA	38.76 (1.33-1131.97)	NA	NA
Type 1 diabetes					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.83 (0.64-1.06)	0.63 (0.47-0.84)	0.51 (0.36-0.73)	0.74 (0.57-0.98)	1.09 (0.77-1.53)
BNT1BNT2	0.49 (0.34-0.71)	0.70 (0.36-1.35)	0.49 (0.22-1.07)	0.60 (0.36-1.01)	0.91 (0.54-1.53)
BNT1BNT2BNT3	0.42 (0.20-0.87)	0.63 (0.29-1.39)	NA	0.24 (0.03-2.05)	0.79 (0.38-1.66)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.90 (0.62-1.28)	0.91 (0.64-1.27)	0.83 (0.52-1.33)	1.04 (0.68-1.61)	1.72 (0.82-3.59)

Table 4c: Sensitivity analyses of the contemporary cohort relative risks of onset of immune-mediated diseases in the 28 day main risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Autoimmune hepatitis					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA
BNT1BNT2	NA	1.98 (0.21-18.88)	NA	NA	1.19 (0.13-10.46)
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	14.25 (1.73-117.51)	NA	NA	NA	10.97 (1.13-106.22)
Guillain-Barré syndrome					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA
BNT1BNT2	NA	NA	NA	NA	NA
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	3.28 (0.27-40.11)	57.37 (8.93-368.40)	33.69 (5.57-203.90)	NA	18.29 (0.78-430.15)
Type 1 diabetes					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.32 (0.99-1.75)	0.84 (0.54-1.29)	1.35 (0.29-6.35)	1.23 (0.88-1.73)	1.42 (0.94-2.14)
BNT1BNT2	1.12 (0.72-1.75)	0.91 (0.57-1.46)	0.92 (0.29-2.89)	0.91 (0.56-1.48)	1.52 (0.97-2.39)
BNT1BNT2BNT3	2.14 (0.29-15.65)	2.43 (0.31-18.87)	NA	NA	1.03 (0.24-4.46)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.36 (0.83-2.20)	1.25 (0.47-3.30)	1.07 (0.66-1.72)	1.50 (0.87-2.58)	2.74 (1.33-5.63)

Table 4d: Sensitivity analyses of the contemporary cohort relative risks of onset of immune-mediated diseases in the 180 day main risk period in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Autoimmune hepatitis					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.70 (0.15-3.25)	0.92 (0.26-3.35)	NA	1.32 (0.20-8.57)	0.44 (0.15-1.27)
BNT1BNT2	1.04 (0.10-10.40)	NA	NA	NA	0.70 (0.07-6.62)
BNT1BNT2BNT3	3.54 (0.11-117.78)	14.74 (1.18-184.93)	NA	NA	2.77 (0.37-20.86)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	3.24 (0.58-18.03)	3.83 (0.53-27.60)	NA	16.05 (1.96-131.58)	2.75 (0.29-26.36)
Guillain-Barré syndrome					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.00 (0.20-5.00)	13.23 (0.12-1416.23)	NA	2.13 (0.06-80.82)	11.42 (0.14-924.50)
BNT1BNT2	NA	NA	NA	NA	NA
BNT1BNT2BNT3	NA	NA	NA	NA	NA
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	2.03 (0.27-15.53)	7.96 (2.28-27.79)	4.47 (1.34-14.90)	6.64 (0.68-64.96)	2.91 (0.15-56.32)
Type 1 diabetes					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.24 (1.03-1.49)	0.96 (0.78-1.18)	1.23 (0.92-1.64)	1.12 (0.88-1.42)	1.30 (1.00-1.69)
BNT1BNT2	0.99 (0.70-1.40)	1.34 (0.58-3.07)	1.36 (0.65-2.82)	1.06 (0.47-2.41)	1.26 (0.83-1.93)
BNT1BNT2BNT3	1.08 (0.56-2.07)	1.78 (0.92-3.47)	NA	1.04 (0.14-7.64)	1.43 (0.80-2.55)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.03 (0.80-1.33)	0.83 (0.64-1.07)	0.85 (0.67-1.08)	1.00 (0.75-1.32)	1.16 (0.77-1.74)

Table 5: Incidence rates (per 100,000 person-years of follow-up) of onset of immune-mediated diseases in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19			All		
Event	**Number of cases**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of cases**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of cases**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of cases**	**Person-years of follow-up**	**Incidence rate (IR)**
Autoimmune hepatitis	15	3479828	0.4	24	1845043	1.3	41	1689633	2.4	80	7014504	1.1
Guillain-Barré syndrome	16	3479767	0.5	14	1845114	0.8	14	1689761	0.8	44	7014642	0.6
Type 1 diabetes	1209	3474016	34.8	1035	1835040	56.4	657	1677523	39.2	2901	6986579	41.5

Table 6: Case counts and contemporary cohort relative risks with associated excess risks per 100,000 vaccinations/infections for onset of immune-mediated disease in the 28 day main risk period stratified by age in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to19		
Exposure	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**
Autoimmune hepatitis									
Unvaccinated	13	1 (ref)	1 (ref)	16	1 (ref)	1 (ref)	25	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA	NA	NA	NA	NA
BNT1BNT2	NA	NA	NA	NA	NA	NA	<5	1.19 (0.13-10.46)	0.07 (-2.76-0.39)
BNT1BNT2BNT3	0	NA	NA	NA	NA	NA	NA	NA	NA
Non-infected	13	1 (ref)	1 (ref)	16	1 (ref)	1 (ref)	25	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	NA	NA	NA	NA	NA	<5	10.97 (1.13-106.22)	3.34 (0.43-3.65)
Guillain-Barré syndrome									
Unvaccinated	16	1 (ref)	1 (ref)	8	1 (ref)	1 (ref)	7	1 (ref)	1 (ref)
BNT1	NA	NA	NA	NA	NA	NA	NA	NA	NA
BNT1BNT2	0	NA	NA	0	NA	NA	NA	NA	NA
BNT1BNT2BNT3	0	NA	NA	0	NA	NA	NA	NA	NA
Non-infected	16	1 (ref)	1 (ref)	8	1 (ref)	1 (ref)	7	1 (ref)	1 (ref)
SARS-CoV-2 infection	<5	33.69 (5.57-203.90)	2.68 (2.27-2.75)	NA	NA	NA	<5	18.29 (0.78-430.15)	3.10 (-0.94-3.27)
Type 1 diabetes									
Unvaccinated	1112	1 (ref)	1 (ref)	712	1 (ref)	1 (ref)	333	1 (ref)	1 (ref)
BNT1	10	1.35 (0.29-6.35)	1.00 (-9.77-3.29)	41	1.23 (0.88-1.73)	0.94 (-0.68-2.09)	29	1.42 (0.94-2.14)	1.03 (-0.24-1.87)
BNT1BNT2	<22	0.92 (0.29-2.89)	-0.53 (-14.68-3.97)	<22	0.91 (0.56-1.48)	-0.34 (-2.68-1.09)	29	1.52 (0.97-2.39)	1.32 (-0.11-2.23)
BNT1BNT2BNT3	NA	NA	NA	NA	NA	NA	<5	1.03 (0.24-4.46)	0.07 (-7.68-1.87)
Non-infected	1112	1 (ref)	1 (ref)	713	1 (ref)	1 (ref)	333	1 (ref)	1 (ref)

Table 6: Case counts and contemporary cohort relative risks with associated excess risks per 100,000 vaccinations/infections for onset of immune-mediated disease in the 28 day main risk period stratified by age in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to19		
Exposure	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**	**Number of cases**	**Relative Risk (95%CI)**	**Excess risk (95%CI)**
SARS-CoV-2 infection	19	1.07 (0.66-1.72)	0.27 (-2.15-1.76)	14	1.50 (0.87-2.58)	1.97 (-0.91-3.65)	8	2.74 (1.33-5.63)	4.88 (1.92-6.33)

Table 7: Case counts and contemporary cohort relative risks with associated excess risks per 100,000 vaccinations/infections for onset of immune-mediated disease in the 180 day main risk period stratified by age in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**
Autoimmune hepatitis									
Unvaccinated	13	1 (ref)	NA	16	1 (ref)	NA	25	1 (ref)	NA
BNT1	NA	NA	NA	<11	1.32 (0.20-8.57)	0.03 (-0.48-0.11)	<11	0.44 (0.15-1.27)	-0.23 (-0.99-0.04)
BNT1BNT2	NA	NA	NA	NA	NA	NA	<5	0.70 (0.07-6.62)	-0.13 (-3.90-0.27)
BNT1BNT2BNT3	0	NA	NA	NA	NA	NA	<5	2.77 (0.37-20.86)	0.36 (-0.97-0.54)
Non-infected	13	1 (ref)	NA	16	1 (ref)	NA	25	1 (ref)	NA
SARS-CoV-2 infection	NA	NA	NA	<5	16.05 (1.96-131.58)	0.45 (0.24-0.48)	<5	2.75 (0.29-26.36)	0.37 (-1.46-0.56)
Guillain-Barré syndrome									
Unvaccinated	16	1 (ref)	NA	8	1 (ref)	NA	7	1 (ref)	NA
BNT1	NA	NA	NA	<6	2.13 (0.06-80.82)	0.10 (-3.17-0.19)	<6	11.42 (0.14-924.50)	0.06 (-0.41-0.07)
BNT1BNT2	0	NA	NA	<5	NA	NA	NA	NA	NA
BNT1BNT2BNT3	0	NA	NA	0	NA	NA	<5	416.13 (0.00-272837075.00)	0.99 (-1567.96-1.00)
Non-infected	16	1 (ref)	NA	8	1 (ref)	NA	7	1 (ref)	NA
SARS-CoV-2 infection	5	4.47 (1.34-14.90)	0.14 (0.05-0.17)	<5	6.64 (0.68-64.96)	0.14 (-0.08-0.17)	<5	2.91 (0.15-56.32)	0.31 (-2.64-0.46)
Type 1 diabetes									
Unvaccinated	1112	1 (ref)	NA	712	1 (ref)	NA	333	1 (ref)	NA
BNT1	60	1.23 (0.92-1.64)	1.04 (-0.51-2.20)	190	1.12 (0.88-1.42)	0.45 (-0.58-1.26)	183	1.30 (1.00-1.69)	0.77 (-0.00-1.36)
BNT1BNT2	8	1.36 (0.65-2.82)	2.33 (-4.72-5.72)	25	1.06 (0.47-2.41)	0.25 (-4.91-2.53)	37	1.26 (0.83-1.93)	0.68 (-0.67-1.55)

Table 7: Case counts and contemporary cohort relative risks with associated excess risks per 100,000 vaccinations/infections for onset of immune-mediated disease in the 180 day main risk period stratified by age in 5-to-19-year-olds in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**	**Number of cases**	**Estimate (95% CI)**	**Excess risk (95% CI)**
BNT1BNT2BNT3	<5	421.39 (54.22-3274.77)	1039.13 (1022.40-1041.29)	<5	1.04 (0.14-7.64)	0.31 (-44.26-6.40)	18	1.43 (0.80-2.55)	0.94 (-0.79-1.90)
Non-infected	1112	1 (ref)	NA	713	1 (ref)	NA	333	1 (ref)	NA
SARS-CoV-2 infection	92	0.85 (0.67-1.08)	-0.59 (-1.63-0.23)	67	1.00 (0.75-1.32)	-0.01 (-1.38-1.03)	30	1.16 (0.77-1.74)	0.46 (-0.99-1.43)

Table 8: Vaccination and infection status at study end among 5-to-19-year-olds in cohorts of patients with pre-existing immune-mediated disease in Denmark, Finland, Norway, and Sweden

Characteristic	EMA/2020/48/TDA/09, Lot 5.04 (%[1])	BNT1 N (%[1])	BNT1BNT2 N (%[1])	BNT1BNT2BNT3 N (%[1])	Other N (%[1])	Infected N (%[1])	Non-infected N (%[1])	Total
Juvenile rheumatoid arthritis patient cohort								
Denmark	450 (23.3%)	70 (3.6%)	1037 (53.8%)	364 (18.9%)	7 (0.4%)	1474 (76.5%)	454 (23.5%)	1928
Finland	1001 (31.2%)	221 (6.9%)	1074 (33.4%)	461 (14.4%)	454 (14.1%)	826 (25.7%)	2385 (74.3%)	3211
Norway	510 (35.7%)	299 (20.9%)	384 (26.9%)	142 (9.9%)	94 (6.6%)	693 (48.5%)	736 (51.5%)	1429
Sweden	391 (18.5%)	70 (3.3%)	1084 (51.3%)	315 (14.9%)	252 (11.9%)	670 (31.7%)	1442 (68.3%)	2112
Girls	1445 (26.6%)	404 (7.4%)	2175 (40.0%)	859 (15.8%)	553 (10.2%)	2307 (42.4%)	3129 (57.6%)	5436
Boys	907 (28.0%)	256 (7.9%)	1404 (43.3%)	423 (13.0%)	254 (7.8%)	1356 (41.8%)	1888 (58.2%)	3244
Age 5 to 11	1366 (65.5%)	237 (11.4%)	473 (22.7%)	9 (0.4%)	<5	899 (43.1%)	1187 (56.9%)	2086
Age 12 to 15	616 (20.2%)	314 (10.3%)	1687 (55.3%)	151 (5.0%)	280 (9.2%)	1267 (41.6%)	1781 (58.4%)	3048
Age 16 to 19	370 (10.4%)	109 (3.1%)	1419 (40.0%)	1122 (31.6%)	526 (14.8%)	1497 (42.2%)	2049 (57.8%)	3546
0 comorbidity	1875 (27.6%)	531 (7.8%)	2829 (41.6%)	949 (14.0%)	613 (9.0%)	2967 (43.7%)	3830 (56.3%)	6797
1 comorbidity	397 (25.1%)	105 (6.6%)	650 (41.1%)	265 (16.8%)	163 (10.3%)	582 (36.8%)	998 (63.2%)	1580
2+ comorbidities	80 (26.4%)	24 (7.9%)	100 (33.0%)	68 (22.4%)	31 (10.2%)	114 (37.6%)	189 (62.4%)	303
Total	2352 (27.1%)	660 (7.6%)	3579 (41.2%)	1282 (14.8%)	807 (9.3%)	3663 (42.2%)	5017 (57.8%)	8680
Multiple sclerosis patient cohort								
Denmark	7 (17.5%)	<5	8 (20.0%)	24 (60.0%)	0 (0.0%)	31 (77.5%)	9 (22.5%)	40
Finland	<5	<5	<5	7 (38.9%)	5 (27.8%)	10 (55.6%)	8 (44.4%)	18
Norway	<5	<5	19 (42.2%)	10 (22.2%)	8 (17.8%)	24 (53.3%)	21 (46.7%)	45
Sweden	14 (23.7%)	<5	20 (33.9%)	17 (28.8%)	7 (11.9%)	18 (30.5%)	41 (69.5%)	59
Girls	16 (14.3%)	<5	35 (31.2%)	43 (38.4%)	15 (13.4%)	57 (50.9%)	55 (49.1%)	112
Boys	11 (22.0%)	<5	15 (30.0%)	15 (30.0%)	5 (10.0%)	26 (52.0%)	24 (48.0%)	50
Age 5 to 11	<5	0 (0.0%)	<5	0 (0.0%)	0 (0.0%)	<5	0 (0.0%)	<5
Age 12 to 15	7 (20.6%)	5 (14.7%)	13 (38.2%)	6 (17.6%)	<5	15 (44.1%)	19 (55.9%)	34
Age 16 to 19	19 (15.1%)	<5	36 (28.6%)	52 (41.3%)	17 (13.5%)	66 (52.4%)	60 (47.6%)	126
0 comorbidity	15 (12.5%)	<5	42 (35.0%)	48 (40.0%)	12 (10.0%)	59 (49.2%)	61 (50.8%)	120
1 comorbidity	10 (28.6%)	<5	7 (20.0%)	9 (25.7%)	7 (20.0%)	21 (60.0%)	14 (40.0%)	35
2+ comorbidities	<5	<5	<5	<5	<5	<5	<5	7

Total	27 (16.7%)	7 (4.3%)	50 (30.9%)	58 (35.8%)	20 (12.3%)	83 (51.2%)	79 (48.8%)	162
Type 1 diabetes patient cohort								
Denmark	557 (18.1%)	85 (2.8%)	1760 (57.1%)	660 (21.4%)	22 (0.7%)	2194 (71.1%)	890 (28.9%)	3084
Finland	1486 (23.8%)	477 (7.6%)	2401 (38.4%)	1190 (19.0%)	698 (11.2%)	1556 (24.9%)	4696 (75.1%)	6252
Norway	1294 (34.5%)	906 (24.1%)	924 (24.6%)	402 (10.7%)	229 (6.1%)	1589 (42.3%)	2166 (57.7%)	3755
Sweden	895 (15.4%)	195 (3.4%)	3094 (53.2%)	981 (16.9%)	649 (11.2%)	1650 (28.4%)	4164 (71.6%)	5814
Girls	1929 (22.2%)	742 (8.5%)	3730 (42.9%)	1503 (17.3%)	797 (9.2%)	3376 (38.8%)	5325 (61.2%)	8701
Boys	2303 (22.6%)	921 (9.0%)	4449 (43.6%)	1730 (17.0%)	801 (7.8%)	3613 (35.4%)	6591 (64.6%)	10204
Age 5 to 11	2252 (62.4%)	463 (12.8%)	871 (24.1%)	19 (0.5%)	6 (0.2%)	1501 (41.6%)	2110 (58.4%)	3611
Age 12 to 15	1177 (17.3%)	947 (13.9%)	3979 (58.4%)	315 (4.6%)	399 (5.9%)	2471 (36.2%)	4346 (63.8%)	6817
Age 16 to 19	803 (9.5%)	253 (3.0%)	3329 (39.3%)	2899 (34.2%)	1193 (14.1%)	3017 (35.6%)	5460 (64.4%)	8477
0 comorbidity	3321 (22.7%)	1339 (9.2%)	6374 (43.6%)	2406 (16.5%)	1163 (8.0%)	5583 (38.2%)	9020 (61.8%)	14603
1 comorbidity	772 (20.6%)	278 (7.4%)	1614 (43.0%)	708 (18.9%)	383 (10.2%)	1233 (32.8%)	2522 (67.2%)	3755
2+ comorbidities	139 (25.4%)	46 (8.4%)	191 (34.9%)	119 (21.8%)	52 (9.5%)	173 (31.6%)	374 (68.4%)	547
Total	4232 (22.4%)	1663 (8.8%)	8179 (43.3%)	3233 (17.1%)	1598 (8.5%)	6989 (37.0%)	11916 (63.0%)	18905

Table 9: Relative risks of hospital visits among 5-to-19-year-old patients with pre-existing immune-mediated disease in the 28 day main risk period in Denmark, Finland, Norway, Sweden in the 1 January 2021 to 31 December 2022 study period

	SCCS analysis		Contemporary cohort analysis		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Countries included in analyses**
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	16982	1 (ref)	17508	1 (ref)	-
BNT1	857	0.99 (0.91-1.08)	857	1.03 (0.95-1.13)	DK, FI, SE, NO
BNT1BNT2	706	1.01 (0.88-1.15)	706	1.08 (0.98-1.19)	DK, FI, SE, NO
BNT1BNT2BNT3	136	0.88 (0.59-1.30)	136	1.06 (0.68-1.65)	DK, FI, SE, NO
Non-infected	17547	1 (ref)	17550	1 (ref)	-
SARS-CoV-2 infection	245	0.91 (0.79-1.05)	245	0.96 (0.85-1.10)	DK, FI, SE, NO
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	345	1 (ref)	364	1 (ref)	-
BNT1	26	1.18 (0.74-1.90)	26	1.03 (0.67-1.58)	DK, FI, SE, NO
BNT1BNT2	29	1.43 (0.88-2.35)	29	1.17 (0.77-1.80)	DK, FI, SE, NO
BNT1BNT2BNT3	8	0.88 (0.37-2.07)	8	0.76 (0.22-2.64)	DK, SE, NO
Non-infected	364	1 (ref)	364	1 (ref)	-
SARS-CoV-2 infection	<5	1.68 (0.53-5.31)	<5	1.49 (0.52-4.24)	SE, NO
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	50368	1 (ref)	51993	1 (ref)	-
BNT1	3170	1.12 (0.94-1.34)	3170	1.07 (0.93-1.24)	DK, FI, SE, NO
BNT1BNT2	2477	1.09 (1.04-1.14)	2477	1.04 (0.97-1.11)	DK, FI, SE, NO
BNT1BNT2BNT3	399	0.94 (0.81-1.09)	399	0.86 (0.75-0.99)	DK, FI, SE, NO
Non-infected	52130	1 (ref)	52156	1 (ref)	-
SARS-CoV-2 infection	663	0.91 (0.80-1.03)	663	0.89 (0.81-0.99)	DK, FI, SE, NO

Table 10: Relative risks of hospital visits among 5-to-19-year-old patients with pre-existing immune-mediated disease in the 180 day main risk period in Denmark, Finland, Norway, Sweden in the 1 January 2021 to 31 December 2022 study period

	SCCS analysis		Contemporary cohort analysis		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Countries included in analyses**
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	16982	1 (ref)	17508	1 (ref)	-
BNT1	5170	1.05 (0.96-1.14)	5170	1.09 (1.03-1.16)	DK, FI, SE, NO
BNT1BNT2	1049	1.04 (0.90-1.19)	1049	1.12 (0.97-1.28)	DK, FI, SE, NO
BNT1BNT2BNT3	437	0.86 (0.66-1.12)	437	0.97 (0.72-1.32)	DK, FI, SE, NO
Non-infected	17547	1 (ref)	17550	1 (ref)	-
SARS-CoV-2 infection	1571	0.99 (0.82-1.20)	1571	1.04 (0.90-1.20)	DK, FI, SE, NO
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	345	1 (ref)	364	1 (ref)	-
BNT1	169	1.03 (0.76-1.41)	169	0.92 (0.72-1.18)	DK, FI, SE, NO
BNT1BNT2	25	0.73 (0.42-1.27)	25	0.63 (0.26-1.52)	DK, FI, SE, NO
BNT1BNT2BNT3	15	0.33 (0.15-0.71)	15	0.46 (0.23-0.92)	DK, FI, SE, NO
Non-infected	364	1 (ref)	364	1 (ref)	-
SARS-CoV-2 infection	42	1.06 (0.61-1.86)	42	0.98 (0.54-1.79)	DK, FI, SE, NO
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	50368	1 (ref)	51993	1 (ref)	-
BNT1	18305	1.10 (1.02-1.18)	18305	1.03 (0.95-1.12)	DK, FI, SE, NO
BNT1BNT2	3919	1.05 (1.01-1.10)	3919	0.99 (0.93-1.05)	DK, FI, SE, NO
BNT1BNT2BNT3	1790	0.93 (0.77-1.11)	1790	0.84 (0.68-1.03)	DK, FI, SE, NO
Non-infected	52130	1 (ref)	52156	1 (ref)	-
SARS-CoV-2 infection	4139	1.00 (0.94-1.06)	4139	0.97 (0.93-1.00)	DK, FI, SE, NO

Table 11a: Sensitivity analyses of the SCCS relative risks of hospitals visits in 5-to-19-year-olds with immune-mediated disease in the 28 day main risk period in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	0.95 (0.83-1.09)	1.00 (0.90-1.12)	0.82 (0.61-1.10)	1.11 (0.94-1.31)	0.96 (0.85-1.09)
BNT1BNT2	0.98 (0.84-1.14)	1.03 (0.89-1.19)	0.86 (0.58-1.30)	0.99 (0.71-1.39)	1.09 (0.95-1.26)
BNT1BNT2BNT3	0.84 (0.41-1.72)	0.99 (0.80-1.24)	NA	1.37 (0.93-2.03)	1.05 (0.65-1.70)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.94 (0.74-1.18)	0.90 (0.75-1.07)	1.00 (0.82-1.23)	0.79 (0.61-1.02)	0.93 (0.68-1.26)
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	3.17 (1.15-8.76)	0.74 (0.40-1.35)	NA	2.00 (0.69-5.82)	1.08 (0.62-1.86)
BNT1BNT2	3.01 (0.88-10.24)	1.16 (0.63-2.13)	NA	17.57 (3.62-85.40)	1.36 (0.69-2.65)
BNT1BNT2BNT3	15.01 (1.78-126.82)	0.72 (0.25-2.07)	NA	NA	0.79 (0.32-1.97)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.22 (0.21-7.01)	1.68 (0.34-8.38)	NA	1.38 (0.11-16.95)	0.86 (0.17-4.29)
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.13 (0.95-1.33)	1.11 (0.91-1.36)	0.90 (0.78-1.03)	1.17 (0.84-1.63)	1.22 (1.05-1.41)
BNT1BNT2	1.09 (1.02-1.16)	1.09 (1.02-1.17)	0.89 (0.74-1.07)	1.20 (0.96-1.49)	1.18 (1.05-1.32)
BNT1BNT2BNT3	0.98 (0.79-1.22)	0.92 (0.75-1.13)	NA	1.25 (0.64-2.42)	1.07 (0.94-1.22)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.88 (0.71-1.10)	0.93 (0.83-1.06)	0.85 (0.69-1.04)	0.92 (0.79-1.08)	1.01 (0.85-1.21)

Table 11b: Sensitivity analyses of the SCCS relative risks of hospitals visits in 5-to-19-year-olds with immune-mediated disease in the 180 day main risk period in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.03 (0.93-1.14)	1.05 (0.95-1.18)	0.93 (0.73-1.18)	1.12 (0.93-1.36)	1.08 (0.99-1.19)
BNT1BNT2	1.02 (0.87-1.20)	1.05 (0.91-1.23)	1.03 (0.76-1.39)	1.17 (0.92-1.48)	1.18 (0.97-1.44)
BNT1BNT2BNT3	0.87 (0.69-1.11)	0.86 (0.62-1.18)	0.47 (0.06-3.67)	1.60 (0.81-3.17)	1.08 (0.80-1.46)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.97 (0.75-1.26)	1.01 (0.86-1.20)	0.98 (0.73-1.31)	0.83 (0.56-1.22)	1.20 (0.73-1.99)
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	2.05 (1.11-3.78)	0.77 (0.53-1.12)	NA	1.73 (0.50-5.96)	0.95 (0.65-1.39)
BNT1BNT2	1.83 (0.50-6.69)	0.44 (0.21-0.93)	NA	0.24 (0.05-1.23)	0.75 (0.38-1.48)
BNT1BNT2BNT3	0.26 (0.03-1.97)	0.30 (0.12-0.72)	NA	NA	0.23 (0.09-0.54)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.60 (0.52-4.91)	0.94 (0.49-1.78)	NA	0.28 (0.02-5.13)	0.93 (0.47-1.85)
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.08 (1.02-1.14)	1.11 (1.01-1.23)	0.93 (0.86-1.02)	1.19 (0.95-1.50)	1.20 (1.08-1.33)
BNT1BNT2	1.06 (1.00-1.12)	1.05 (0.98-1.12)	0.88 (0.74-1.04)	1.22 (1.06-1.41)	1.17 (1.03-1.34)
BNT1BNT2BNT3	0.96 (0.83-1.12)	0.90 (0.73-1.11)	0.91 (0.11-7.31)	1.11 (0.67-1.84)	1.09 (0.89-1.34)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.98 (0.89-1.07)	1.03 (0.96-1.10)	0.95 (0.88-1.02)	0.97 (0.89-1.07)	1.16 (0.96-1.39)

Table 11c: Sensitivity analyses of the contemporary cohort relative risks of hospitals visits in 5-to-19-year-olds with immune-mediated disease in the 28 day main risk period in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.02 (0.90-1.16)	1.04 (0.93-1.16)	0.91 (0.74-1.11)	1.10 (0.97-1.25)	1.01 (0.90-1.13)
BNT1BNT2	1.07 (0.87-1.32)	1.08 (0.98-1.19)	0.95 (0.69-1.31)	1.03 (0.85-1.26)	1.16 (1.02-1.31)
BNT1BNT2BNT3	0.98 (0.42-2.27)	1.20 (0.97-1.47)	NA	1.58 (1.10-2.25)	1.18 (0.69-2.00)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.03 (0.83-1.28)	0.93 (0.79-1.09)	1.04 (0.86-1.25)	0.85 (0.68-1.08)	0.94 (0.72-1.24)
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	2.69 (1.08-6.69)	0.67 (0.39-1.18)	NA	1.62 (0.58-4.50)	1.04 (0.64-1.71)
BNT1BNT2	2.66 (1.02-6.95)	0.87 (0.50-1.51)	NA	10.27 (2.42-43.54)	1.21 (0.72-2.04)
BNT1BNT2BNT3	22.93 (5.22-100.83)	0.41 (0.16-1.08)	NA	NA	0.74 (0.22-2.52)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.66 (0.37-7.41)	1.56 (0.34-7.14)	NA	2.12 (0.15-29.66)	0.71 (0.17-2.96)
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.08 (0.93-1.25)	1.06 (0.91-1.23)	0.92 (0.81-1.04)	1.12 (0.85-1.47)	1.11 (1.00-1.24)
BNT1BNT2	1.03 (0.94-1.12)	1.04 (0.98-1.12)	0.93 (0.71-1.22)	1.12 (0.88-1.42)	1.05 (0.98-1.12)
BNT1BNT2BNT3	0.88 (0.76-1.01)	0.83 (0.65-1.05)	NA	1.12 (0.66-1.89)	0.81 (0.72-0.91)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.87 (0.72-1.05)	0.91 (0.81-1.02)	0.85 (0.74-0.98)	0.93 (0.80-1.09)	0.94 (0.81-1.09)

Table 11d: Sensitivity analyses of the contemporary cohort relative risks of hospitals visits in 5-to-19-year-olds with immune-mediated disease in the 180 day main risk period in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

Exposure	Boys	Girls	Age 5 to 11	Age 12 to 15	Age 16 to 19
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.10 (0.95-1.27)	1.10 (1.04-1.16)	1.04 (0.90-1.20)	1.08 (0.97-1.20)	1.14 (1.06-1.22)
BNT1BNT2	1.14 (0.85-1.52)	1.12 (1.03-1.22)	1.18 (0.93-1.49)	1.16 (0.93-1.45)	1.24 (1.04-1.47)
BNT1BNT2BNT3	0.94 (0.71-1.25)	1.00 (0.72-1.41)	1.67 (0.23-12.10)	1.77 (0.84-3.74)	1.12 (0.76-1.64)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	1.03 (0.84-1.27)	1.05 (0.93-1.19)	1.02 (0.79-1.30)	0.98 (0.83-1.16)	1.16 (1.04-1.30)
Multiple sclerosis visits among multiple sclerosis patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.58 (0.92-2.70)	0.72 (0.53-0.99)	NA	1.60 (0.84-3.06)	0.94 (0.70-1.26)
BNT1BNT2	1.55 (0.47-5.13)	0.43 (0.13-1.40)	NA	0.32 (0.06-1.58)	0.81 (0.33-2.01)
BNT1BNT2BNT3	0.67 (0.13-3.41)	0.35 (0.14-0.93)	NA	NA	0.40 (0.17-0.97)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.41 (0.03-5.05)	1.12 (0.58-2.13)	NA	0.44 (0.02-10.05)	0.99 (0.55-1.81)
Type 1 diabetes visits among type 1 diabetes patients					
Unvaccinated	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
BNT1	1.02 (0.94-1.10)	1.05 (0.96-1.14)	0.92 (0.82-1.04)	1.11 (0.92-1.35)	1.05 (1.00-1.11)
BNT1BNT2	0.99 (0.90-1.10)	0.99 (0.94-1.05)	0.92 (0.79-1.09)	1.09 (0.97-1.23)	0.96 (0.90-1.03)
BNT1BNT2BNT3	0.86 (0.71-1.04)	0.82 (0.66-1.03)	0.86 (0.12-6.16)	1.13 (0.98-1.29)	0.78 (0.67-0.91)
Non-infected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
SARS-CoV-2 infection	0.94 (0.87-1.01)	1.00 (0.94-1.05)	0.92 (0.87-0.98)	0.97 (0.92-1.03)	1.04 (0.91-1.20)

Table 12: Incidence rates (per person-year of follow-up) of hospital visits among 5-to-19-year-old patients with immune-mediated disease in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5-11			Age 12-15			Age 16-19			All		
Event	**Number of visits**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of visits**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of visits**	**Person-years of follow-up**	**Incidence rate (IR)**	**Number of visits**	**Person-years of follow-up**	**Incidence rate (IR)**
Juvenile rheumatoid arthritis	7597	2170.0	3.5	10174	3361.1	3.0	9009	4107.2	2.2	26780	9638.3	2.8
Multiple sclerosis	8	1.4	5.8	135	27.9	4.8	420	99.7	4.2	563	129	4.4
Type 1 diabetes	18869	3363.6	5.6	31858	6733.9	4.7	33541	9080.2	3.7	84268	19177.4	4.4

Table 13: Hospital visit counts and contemporary cohort relative risks with associated excess risks per 1000 vaccinations/infections in the 28 day main risk period stratified by age in 5-to-19-year-old patients with immune-mediated disease in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**
Juvenile rheumatoid arthritis visits among juvenile rheumatoid arthritis patients									
Unvaccinated	6814	1 (ref)	1 (ref)	6409	1 (ref)	1 (ref)	4285	1 (ref)	1 (ref)
BNT1	108	0.91 (0.74-1.11)	-29.02 (-97.52-27.10)	399	1.10 (0.97-1.25)	22.12 (-7.39-48.12)	350	1.01 (0.90-1.13)	0.80 (-18.58-18.07)
BNT1BNT2	59	0.95 (0.69-1.31)	-15.48(-135.67-71.46)	298	1.03 (0.85-1.26)	7.79 (-42.97-49.53)	349	1.16 (1.02-1.31)	23.35 (4.05-40.40)
BNT1BNT2BNT3	NA	NA	NA	32	1.58 (1.10-2.25)	158.44 (40.94-240.72)	104	1.18 (0.69-2.00)	29.01 (-86.56-96.85)
Non-infected	6820	1 (ref)	1 (ref)	6429	1 (ref)	1 (ref)	4301	1 (ref)	1 (ref)
SARS-CoV-2 infection	117	1.04 (0.86-1.25)	9.85 (-45.66-55.75)	76	0.85 (0.68-1.08)	-35.89 (-100.12-14.97)	52	0.94 (0.72-1.24)	-9.89 (-65.63-32.37)
Multiple sclerosis visits among multiple sclerosis patients									
Unvaccinated	8	1 (ref)	1 (ref)	100	1 (ref)	1 (ref)	256	1 (ref)	1 (ref)
BNT1	NA	NA	NA	5	1.62 (0.58-4.50)	207.21 (-384.87-420.41)	21	1.04 (0.64-1.71)	15.19 (-200.30-147.02)
BNT1BNT2	NA	NA	NA	<28	10.27 (2.42-43.54)	1465.36 (953.29-1586.15)	<28	1.21 (0.72-2.04)	77.14 (-168.24-222.95)
BNT1BNT2BNT3	NA	NA	NA	NA	NA	NA	8	0.74 (0.22-2.52)	-126.42 (-1295.52-216.88)
Non-infected	8	1 (ref)	1 (ref)	100	1 (ref)	1 (ref)	256	1 (ref)	1 (ref)
SARS-CoV-2 infection	NA	NA	NA	<5	2.12 (0.15-29.66)	448.96 (-4724.52-819.54)	<5	0.71 (0.17-2.96)	-108.25 (-1284.36-173.24)

Table 13: Hospital visit counts and contemporary cohort relative risks with associated excess risks per 1000 vaccinations/infections in the 28 day main risk period stratified by age in 5-to-19-year-old patients with immune-mediated disease in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**
Type 1 diabetes visits among type 1 diabetes patients									
Unvaccinated	16854	1 (ref)	1 (ref)	19685	1 (ref)	1 (ref)	15454	1 (ref)	1 (ref)
BNT1	264	0.92 (0.81-1.04)	-36.16 (-96.10 -16.52)	1381	1.12 (0.85-1.47)	39.64 (-65.76-119.94)	1525	1.11 (1.00-1.24)	33.99 (1.37-63.38)
BNT1BNT2	146	0.93 (0.71-1.22)	-30.16 (-166.94 -74.62)	1008	1.12 (0.88-1.42)	41.56 (-51.68-115.15)	1323	1.05 (0.98-1.12)	12.51 (-7.21-30.91)
BNT1BNT2BNT3	NA	NA	NA	52	1.12 (0.66-1.89)	40.90 (-195.57-181.16)	347	0.81 (0.72-0.91)	-64.05 (-105.45—27.13)
Non-infected	16865	1 (ref)	1 (ref)	19764	1 (ref)	1 (ref)	15527	1 (ref)	1 (ref)
SARS-CoV-2 infection	264	0.85 (0.74-0.98)	-69.07 (-141.70—6.25)	225	0.93 (0.80-1.09)	-26.23 (-88.65-27)	174	0.94 (0.81-1.09)	-18.54 (-68.72-24.57)

Table 14: Hospital visit counts and contemporary cohort relative risks with associated excess risks per 1000 vaccinations/infections in the 180 day main risk period stratified by age in 5-to-19-year-old patients with immune-mediated disease in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**
Juvenile rheumatoid arthritis									
Unvaccinated	6814	1 (ref)	NA	6409	1 (ref)	NA	4285	1 (ref)	NA
BNT1	519	1.04 (0.90-1.20)	12.37 (-31.40-50.31)	2179	1.08 (0.97-1.20)	17.70 (-8.07-40.84)	2472	1.14 (1.06-1.22)	21.00 (10.01 - 31.25)
BNT1BNT2	82	1.18 (0.93-1.49)	43.60 (-21.85-95.38)	346	1.16 (0.93-1.45)	35.20 (-17.58-77.57)	621	1.24 (1.04-1.47)	34.52 (7.25-57.51)
BNT1BNT2BNT3	<79	1.67 (0.23-12.10)	249.87 (-2072.18-570.71)	<79	1.77 (0.84-3.74)	134.72 (-57.66-226.09)	358	1.12 (0.76-1.64)	17.13 (-52.26-64.45)
Non-infected	6820	1 (ref)	NA	6429	1 (ref)	NA	4301	1 (ref)	NA
SARS-CoV-2 infection	675	1.02 (0.79-1.30)	4.24 (-67.70 - 60.39)	532	0.98 (0.83-1.16)	-3.70 (-46.12 - 32.12)	364	1.16 (1.04-1.30)	25.74 (6.78-42.67)
Multiple sclerosis									
Unvaccinated	8	1 (ref)	NA	100	1 (ref)	NA	256	1 (ref)	NA
BNT1	NA	NA	NA	34	1.60 (0.84-3.06)	145.60 (-74.01-260.68)	135	0.94 (0.70-1.26)	-24.81 (-161.33 -76.73)
BNT1BNT2	NA	NA	NA	<25	0.32 (0.06-1.58)	-812.45 (-5531.06-138.30)	<25	0.81 (0.33-2.01)	-83.20 (-739.34-182.87)
BNT1BNT2BNT3	NA	NA	NA	NA	NA	NA	12	0.40 (0.17-0.97)	-267.82 (-902.53—5.07)
Non-infected	8	1 (ref)	NA	100	1 (ref)	NA	256	1 (ref)	NA
SARS-CoV-2 infection	NA	NA	NA	<36	0.44 (0.02-10.05)	-373.05 (-14910.46-264.55)	<36	0.99 (0.55-1.81)	-237.72 (-366.55-197.29)
Type 1 diabetes									

Table 14: Hospital visit counts and contemporary cohort relative risks with associated excess risks per 1000 vaccinations/infections in the 180 day main risk period stratified by age in 5-to-19-year-old patients with immune-mediated disease in Denmark, Finland, Norway, and Sweden in the 1 January 2021 to 31 December 2022 study period

	Age 5 to 11			Age 12 to 15			Age 16 to 19		
Exposure	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**	**Number of visits**	**Relative risk (95% CI)**	**Excess risk (95% CI)**
Unvaccinated	16854	1 (ref)	NA	19685	1 (ref)	NA	15454	1 (ref)	NA
BNT1	1263	0.92 (0.82-1.04)	-32.55 (-84.75 -14.01)	7554	1.11 (0.92-1.35)	39.43 (-34.74 - 100.65)	9488	1.05 (1.00-1.11)	15.43 (-0.22-30.26)
BNT1BNT2	179	0.92 (0.79-1.09)	-27.62 (-91.11-26.43)	1139	1.09 (0.97-1.23)	30.15 (-11.10-66.77)	2601	0.96 (0.90-1.03)	-11.73 (-33.57-8.67)
BNT1BNT2BNT3	<261	0.86 (0.12-6.16)	-85.98 (-3825.01-434.39)	<261	1.13 (0.98-1.29)	44.31 (-8.45-90.20)	1529	0.78 (0.67-0.91)	-71.59(-126.47—24.67)
Non-infected	16865	1 (ref)	NA	19764	1 (ref)	NA	15527	1 (ref)	NA
SARS-CoV-2 infection	1531	0.92 (0.87-0.98)	-34.02 (-61.16 —8.46)	1488	0.97 (0.92-1.03)	-9.97(-31.76 - 10.57)	1120	1.04 (0.91-1.20)	12.17 (-29.22-48.28)

Figure 1: Number of patients with immune-mediated disease according to number of hospital visits during the 1 January 2021 to 31 December 2022 study period in Denmark, Finland, Norway and Sweden

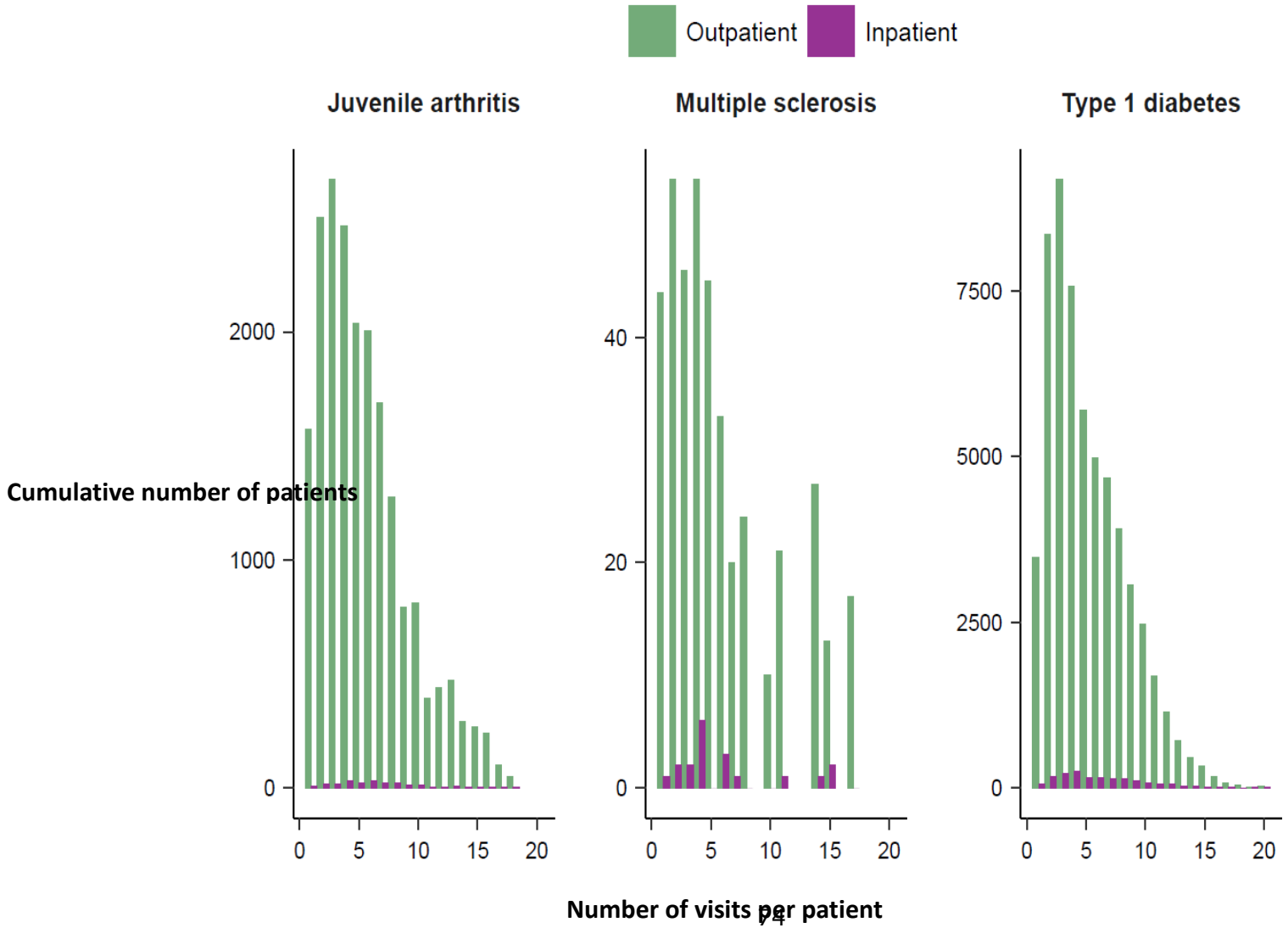
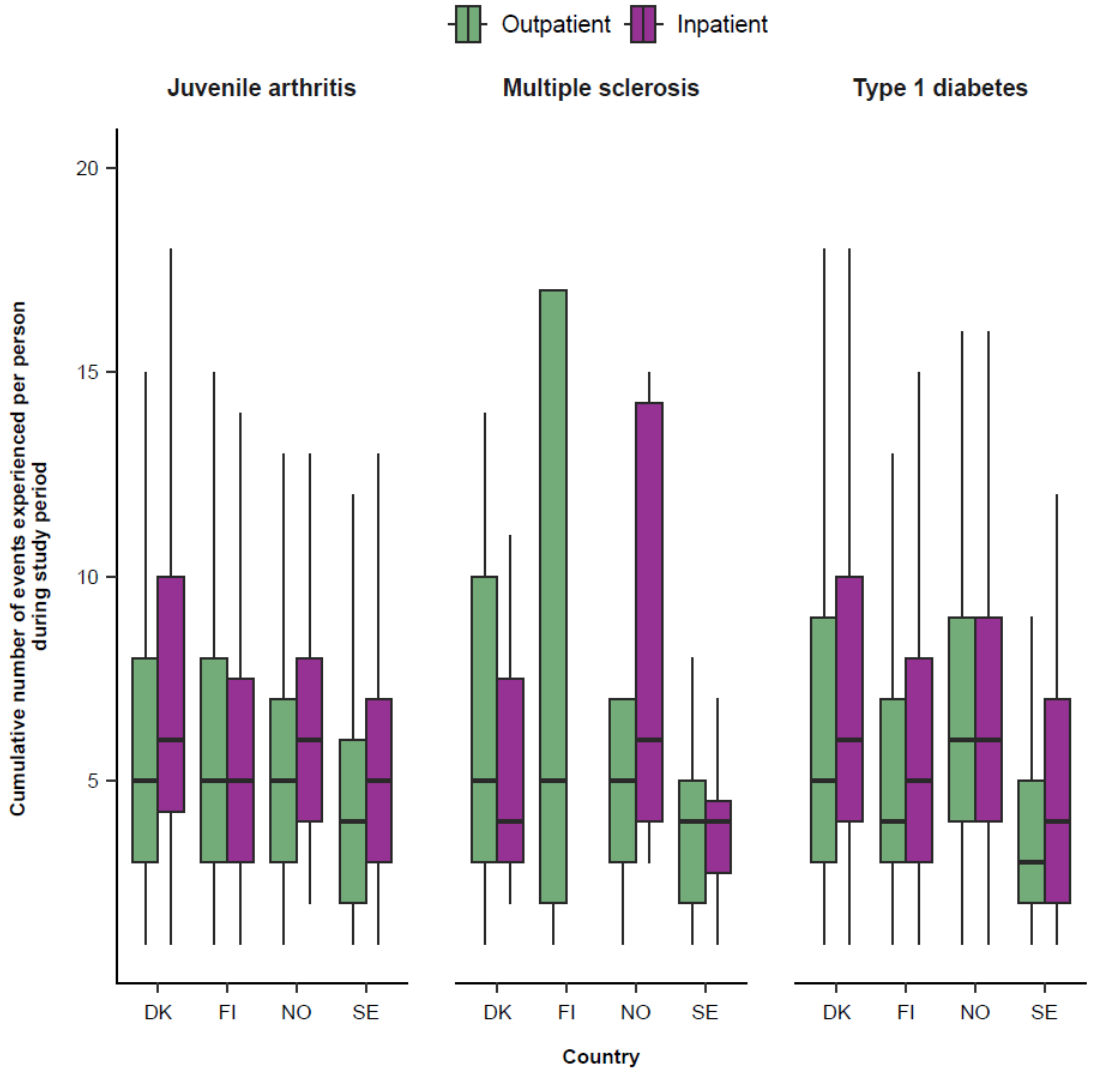


Figure 2: Distribution of number of hospital visits per patient with immune-mediated disease according to patient type and country during the 1 January 2021 to 31 December 2022 study period in Denmark, Finland, Norway and Sweden



10.4 Adverse events / adverse reactions

Not applicable.

11. DISCUSSION

11.1 Key results

New onset immune-mediated disease

In this large Nordic cohort study of COVID-19 vaccination in 5-to-19-year-olds and new onset of autoimmune hepatitis, Guillain-Barré syndrome and type 1 diabetes, we did not observe any robust support for associations between the BNT-vaccine and the selected immune-mediated conditions in either the 28-day- or the 180-day main risk period.

We did observe strong but statistically imprecise associations between infection and Guillain-Barré syndrome. The association was strongest in the 28-day main risk period (contemporary cohort RR 15.10, 95% CI, 1.11-205.94) but still present in the 180-day main risk periods (contemporary cohort RR 3.85, 1.33-11.14).

Immune-mediated disease flares

In three Nordic cohorts of 5-to-19-year-old juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes patients we observed no robust support for an increased risk of hospital visits following BNT vaccination or infection in either the 28-day- or the 180-day main risk period.

11.2 Limitations and methodological considerations

A number of limitations should be considered carefully when evaluating our study results or when planning similar observational studies of the safety of childhood vaccination with respect to immune-mediated diseases.

Statistical power

Most immune-mediated disease occurring in childhood and adolescence are rare. Despite combining nationwide register data from four countries, new onset of the study outcomes was still rare and especially so in the 28-day main risk periods following vaccination and infection. Lack of statistical precision was a particular issue for autoimmune hepatitis and Guillain-Barré syndrome. In most comparisons involving new onset of these two outcomes, the confidence intervals were wide and compatible with both protective effects and increased risks. The statistical precision of the type 1 diabetes estimates allowed us to rule out moderate-to-large increases in risk in the main analyses.

Our meta-analysis approach has the limitation that when pooling the relative risk estimates, we are not able to utilise estimates from a country if there are no study outcomes in either the main-risk or unvaccinated periods. As the main-risk periods are

shorter than the unvaccinated periods, this exclusion is more likely to be due to no events in the main risk period, which leads to underrepresentation of the follow-up time during the main risk period in the meta-analysis. This will, in turn, tend towards an overestimation of the relative risks of the study outcomes. Thus, combined results not based on information from all participating countries should be carefully interpreted taking this into account. The sensitivity analyses where we further stratify by age group and sex are particularly prone to this issue.

We recommend that these are only used to further describe associations identified in the main analyses, and that they are not taken as support for associations by themselves.

The statistical precision of the associations between COVID-19 vaccination or infection and risk of hospital visits in patient cohorts was high enough to exclude moderate-to-large increases in the 180-day main risk period. In the evaluation of the 28-day main risk period, we were also able to rule out moderate-to-large increases in risk of hospital visits, especially for juvenile rheumatoid arthritis and type 1 diabetes patients, and after BNT1 and BNT1BNT2.

Multiple testing

We do not take multiple testing into account in our presentation of statistical precision. We evaluated the associations between 3 exposure categories (in the evaluation of vaccination, BNT1, BNT1BNT2 and BNT1BNT2BNT3), 3 study outcomes and 2 main risk periods using 2 different analytical approaches. Assuming independence between these 36 analyses, we would expect almost 2 false-positive association by chance alone. The issue of multiple testing is further compounded in the sex-, and age group stratified subgroup analyses. This reinforces our statement above, that subgroup analyses should be considered primarily descriptive. This is particularly warranted where we do not observe an association in the main analysis.

In studies such as this without well-supported pre-specified hypotheses of associations, false discovery rate control can be considered, and implemented using e.g. Benjamini-Hochberg adjusted p-values.[37] However, we do not recommend that they are used to indicate an association or the lack of an association by themselves.

Analytical approaches

A strength of our study is the use of two different complementary analytical approaches. However, each approach has limitations that warrants mentioning. The SCCS analysis relies on the assumption that experiencing a study outcome is not related to future vaccination propensity, so-called event-independent exposure. We do utilise a 14-day pre-risk period, but cannot discount that experiencing a study outcome delays or even contra-indicates vaccination beyond 14-days. In the most likely scenario where

vaccination propensity decreases after an outcome, the resulting bias will be in the direction of an increased risk in the main risk period. Although, it is also possible that a new diagnosis of an immune-mediated disease may lead to vaccination.

An alternative to using the SCCS method with a pre-risk period, is to use the modified SCCS method for event-dependent exposures.[38] The modified method allows for events which contraindicates exposure or prevents further observation such as death. However, this comes at a cost. The modified method is less statistically efficient which may be important issue when studying rare events. In our setting, the SCCS method is complemented by the contemporary cohort analysis. The results observed across the different methods were broadly compatible, which supports the internal validity of our results, also from the standard SCCS method.

The contemporary cohort analysis assumes that all potential confounding is addressed by the inclusion of covariates in the regression model. A main source of potential confounding is confounding-by-indication whereby children and adolescents at high risk of severe COVID-19 due to underlying health conditions are offered vaccination before or with more doses than the general 5-to-19-year old population. These underlying health conditions might also be risk factors for the study outcomes. We do include adjustment for comorbidities, but cannot exclude residual confounding, especially in the evaluations of BNT1BNT2BNT3.

We recommend the use of multiple supplementary statistical approaches to increase internal validity. Ideally, results should be consistent across methods. Diverging results can indicate bias or confounding.

New onset of immune-mediated disease

The validity of the hospital-register data and the diagnoses used is considered high.[23,39] However, for many autoimmune diseases the onset is not sudden but more insidious. Thus, there may be significant lag between disease onset, symptom onset and diagnosis. Date of diagnosis (defined as date of admission) is the only information that we have from the hospitalisation registers. This should be carefully considered, especially when using short main risk periods such as a 28-day main risk period. Short risk periods are not well-suited for the detection of increased risks of immune-mediated disease when lag is suspected. In our study, type 1 diabetes is an example of an outcome where we anticipate lag between disease onset, symptom onset and diagnosis. Thus, an increased risk in a 28-day main risk period is unlikely to be causal. At best it could indicate that the exposure has triggered severe symptoms such as ketoacidosis. It could also indicate bias in the form of unmasking, whereby less severe symptoms discussed at a vaccination visit with a health practitioner triggers further diagnostic workup resulting in diagnosis.[40]

We recommend that longer main risk periods are included to account for this lag. The exact duration of longer main risk periods can be difficult to pre-specify and misspecification can lead to bias. Data-driven approaches have been proposed to identify optimal risk periods, but limitations do exist when outcomes are rare.[41] If data-driven approaches are used in the setting of rare immune-mediated diseases, we recommend that they are included only in a descriptive capacity and supplemented with pre-specified risk periods of different lengths.

Date of symptom onset can be sourced from disease-specific registers[42] or by chart review. However, exact dates of symptom onset are unlikely to be available or precise, disease-specific register information will be delayed compared to hospital registers since validation is typically involved, and chart review is resource-demanding, time-consuming and there is no guarantee that it yields the desired information.

Disease flares

We have used hospital visits in patient cohorts as a measure of disease flares. However, in patients with diagnosed immune-mediated disease, hospital visits for routine check-ups are not uncommon. In the study period, the average rates of hospital visits per year were 2.8, 4.4 and 4.4 per year of follow-up, for juvenile rheumatoid arthritis, multiple sclerosis and type 1 diabetes, respectively. Thus, the increase in hospital visits caused by increased disease activity that can be reliably detected should be considered. The highest upper bound of the estimated confidence intervals in the evaluation of hospital contacts in the 180-day main risk period was 1.79 (multiple sclerosis visits among multiple sclerosis patients following infection, Table 10). This is equivalent to an excess of visits of approximately 1.7 per 180-days. Disease registers may also contain info on disease progression, but the same limitations as stated above apply.

If an increased risk of hospital visits is observed, it is recommended to also consider alternative explanations to disease flares. As an example, if routine vaccination visits in childhood coincide with general health check-ups, this may also among patient populations prompt further disease specific evaluations e.g. in relation to drug treatment strategies and result in unmasking bias.

Using hospital visits as a proxy for disease activity is feasible. But alternative explanations for an increase in hospital visits should be carefully evaluated.

Routine childhood vaccination and risk of immune-mediated diseases

Childhood vaccines are often administered very early in life, often in infancy. In that sense, COVID-19 vaccination of children and adolescents closely resembles human papillomavirus vaccination. If studies of early childhood vaccinations and immune-mediated disease is planned, we recommend that less reliance is given towards the

SCCS method and short- to moderate-term main risk periods. The age of onset of the majority of immune-mediated diseases is not in infancy, and instead more conventional vaccinated vs unvaccinated designs should be preferred allowing for more long-term evaluations of risk throughout childhood.

Data-sources outside of the Nordic countries

Few countries outside of the Nordics have nationwide population-based registers going back decades. Alternative data-sources might be primary-care databases, regional databases, and health-care provide databases. Key limitations of these data-sources in comparison to the Nordic registers are that further linkage to other data sources is often not possible, that individuals may be lost to follow-up by moving or changing health-care provider, and that generalisability may be lost due to the selected populations included. When ascertaining new onset of disease, it may not be possible to use longer look-back periods, which increases the risk of including prevalent cases as incident cases. If exposures and outcomes can also be ascertained outside of a database, there is a risk that spurious associations can be introduced due to information bias. Many immune-mediated outcomes will not be diagnosed in primary care, and, thus, it is imperative that these data-sources are linked to hospital-records. Finally, the study of rare events benefits from combining data-sources to increase statistical power. Outside of the Nordic countries this may mean combining heterogenous data-sources and using statistical methods that do not fully take into account limitations and strengths of each source.

Summary of recommendations

- Multi-country collaborations using meta-analyses of single country results can be conducted more rapidly in contrast to collaborations which combine data before analysis. However, meta-analysed associations of very rare events are susceptible to bias when single country associations cannot be estimated and included in the meta-analysis due to no events. This should be taken into account when interpreting results.
- This is a particular issue for stratified analyses. We recommend that these are only used to further describe associations identified in the main analyses, and that they are not taken as support for associations by themselves.
- Multiple testing is an issue in safety studies evaluating several outcomes. In studies without well-supported pre-specified hypotheses of associations, false discovery rate control can be considered, and implemented using e.g. Benjamini-Hochberg adjusted p-values. However, we do not recommend that they are used to indicate an association or the lack of an association by themselves.
- There may be significant lag between onset of symptoms and diagnosis. We recommend that longer main risk periods are included to account for this lag. The

exact duration of longer main risk periods can be difficult to pre-specify and misspecification can lead to bias. Data-driven approaches have been proposed to identify optimal risk periods. If data-driven approaches are used in the setting of rare immune-mediated diseases, we recommend that they are included only in a descriptive capacity and supplemented with pre-specified risk periods of different lengths.

- Using hospital visits as a proxy for disease activity is feasible. But alternative explanations for an increase in hospital visits should be carefully evaluated.
- When studying flares using designs which compares different time periods, it is critical to ensure that recurring outcomes are ascertained in exactly the same way between periods.
- If studies of early childhood vaccinations and immune-mediated disease is planned, we recommend that less reliance is given towards the SCCS method and short- to moderate-term main risk periods. The age of onset of the majority of immune-mediated diseases is not in infancy, and instead more conventional vaccinated vs unvaccinated designs should be preferred allowing for more long-term evaluations of risk throughout childhood.
- Using data-source that do not resemble the Nordic registers and in multi-site collaborations between heterogeneous databases, a number of limitations must be considered in relation to the identification of new onset of disease, the generalisability of results and the possibility of information bias.

11.3 Interpretations

In a Nordic cohort of 5 million 5-to-19-year-olds with 2.4 million vaccinated (Table 1), we reassuringly found no robust evidence for associations between BNT vaccination and a) new onset of autoimmune hepatitis, Guillain-Barré syndrome and type 1 diabetes, or b) recurrent hospital visits for juvenile rheumatoid arthritis, multiple sclerosis and type diabetes in patient cohorts. The results from two different analytical approaches complement each other and support the internal validity of our study.

Very few studies have evaluated the safety of COVID-19 vaccination in children and adolescents with respect to immune-mediated diseases. This is probably partly due to the limited use of COVID-19 vaccination in children globally and the rarity of immune-mediated events.

In a summary of case-series, autoimmune hepatitis occurred in adults with onset on day 1 to day 31 after vaccination.[43] However, case series with temporal relationships are not sufficient for causality and we are not aware of observational studies comparing risks in vaccinated and unvaccinated.

The COVID-19 vaccines have been linked to Guillain-Barré syndrome. In a Vaccine Safety Datalink study of individuals 12-years or older, the viral vector vaccine, Ad.26.COV2.S, but not the mRNA vaccines, was associated with Guillain-Barré syndrome.[44] This finding is supported by a large observed vs expected analysis in the US Vaccine Adverse Event Reporting System, where no increased reporting rate was observed following the mRNA vaccines.[45] In a Korean study, also using passive surveillance reports, a ratio of 3.7 comparing rates of Guillain-Barré syndrome reports between viral vector- and mRNA vaccines was reported.[46] The majority of events were reported in individuals 30-years or older. In an English SCCS study, an association between the first dose of ChAdOx1 and Guillain-Barré syndrome, but not the mRNA vaccines was reported.[47] In an observed vs expected analysis in UK and Spanish primary care data databases, there was no association between viral vector- or mRNA vaccines, and Guillain-Barré syndrome.[10] However, this was in general populations with median ages of 48 and 47 years. We observed strong, but statistically imprecise, associations between COVID-19 infection and Guillain-Barré syndrome. The association was observed in both the 28-day- and in the 180-day main risk periods. This is consistent with other reports in older adults.[10]

Studies evaluating an association between vaccination and type 1 diabetes is very sparse and seems to be restricted to rare case reports of adult onset disease.[48]

Similarly, evidence supporting associations between COVID-19 vaccination and disease flares in patient populations is rare. A short clinical follow-up study of 43 children with juvenile rheumatoid arthritis in Poland did not report exacerbations of disease.[49] This was also the conclusion of a follow-up of 99 juvenile rheumatoid arthritis patients in Turkey.[50] In a follow-up of 30 patients with paediatric onset multiple sclerosis, no relapses were observed after vaccination.[51] Among 70 children and adolescents with type 1 diabetes and wearing a continuous glucose monitor, vaccination was not associated with acute glucose imbalances.[52]

We have identified no studies with controlled comparisons of disease flares in vaccinated and unvaccinated children and adolescents.

11.4 Generalisability

Our study is based on the general 5-to-19-year-old populations in four countries and, thus, our results have a high degree of generalisability to other general 5-to-19-year old populations by design. However, our results, only inform on the safety of BNT1, BNT1BNT2 and BNT1BNT2BNT3, and not on other vaccines that have been used in this population (in comparable countries, this would primarily be mRNA-1273 in the 16-to-

19-year-olds). It should also be mentioned that BNT1BNT2BNT3 was almost exclusively used in 16-to-19-year olds, and we cannot inform on the risks of BNT1BNT2BNT3 in the younger age groups. It is also noteworthy that vaccine uptake was low in 5-to-11-year-olds and our results on BNT1 and BNT1BNT2, thus, primarily informs on vaccine safety in 12-to-19-year-olds.

12. OTHER INFORMATION

None.

13. CONCLUSION

Autoimmune hepatitis, Guillain-Barré syndrome and type 1 diabetes were rare after COVID-19 vaccination with BNT among 5-to-19-year-olds in the Nordic countries during 1 January 2021 to 31 December 2022. We did not observe any robust associations between BNT1, BN1BNT2 or BNT1BNT2BNT3 and new onset of these three immune-mediated diseases in either the 28-day- or the 180-day main risk periods. We did identify a strong, but statistically imprecise, association between SARS-CoV-2 infection and Guillain-Barré syndrome in both the 28-day- and the 180-day main risk periods. This association has previously been observed in adults,[10] but to our knowledge, this is the first time it has been observed in children and adolescents.

We found no robust support for increased disease activity following BNT vaccination or among juvenile rheumatoid arthritis, multiple sclerosis or type 1 diabetes patients in either the 28-day- or the 180-day main risk periods.

The study of immune-mediated diseases in the observational setting has a number of limitations. Foremost, is the lag between disease onset, symptom onset and first diagnosis. This requires careful consideration of main risk period definitions and careful interpretation of results. The evaluation of risk of disease flares is limited by the lack of available information on disease activity outside of chart review and detailed disease specific registers or databases. The alternative use of hospital visits is feasible but requires careful consideration of alternative explanations of any observed increases.

In conclusion, the current study provides much needed and reassuring evidence supporting that BNT vaccination is not associated with immune-mediated disease onset or activity in children and adolescents.

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